THERAPEUTIC CANNABIS USE FOR SLEEP AND MENTAL HEALTH

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Lay Abstract

Recent changes to worldwide cannabis policies have led to cannabis use becoming more common. Among individuals who use cannabis to manage medical conditions, many report sleep and mental health as the main reasons for use. While more individuals are turning to cannabis for therapeutic use, very little is known about how it is used and what effects it may have. For our research, we examined large databases of cannabis users to understand patterns of cannabis use for sleep and mental health. We also investigated how individuals with the most frequently reported mental health concerns (insomnia, depression, and anxiety) reported feeling after cannabis use. We found that individuals who used cannabis for insomnia symptoms, with or without another mental health concern, reported general improvements in sleep. Some types of cannabis were also reported to work better than other types of cannabis. In addition, we found unique patterns in how individuals with insomnia, depression, or anxiety reported feeling after cannabis use. Although our overall results may seem positive, more research is needed to specifically understand how cannabis works, and whether it can be used safely for sleep and mental health conditions.

Abstract

Introduction: The evolving global landscape around cannabis regulation has renewed interest in exploring the therapeutic potential of cannabinoids for several medical conditions. Of these conditions, sleep and mental health concerns are often reported among the most common reasons for therapeutic cannabis use. In this work, we investigated the patterns and profiles of cannabis use in naturalistic samples to better understand its use for the management of sleep and mental health symptoms. We focused our examination on insomnia, depression, and anxiety, as cannabis is most often used to manage these conditions.

Results: Across our studies, cannabis was generally perceived to be efficacious for the management of insomnia symptoms in various mental health conditions. Analyses of strain categories revealed differences in perceived symptom improvement between strains for some conditions. In individuals with insomnia, indica-dominant and indica hybrid strains were found to reduce insomnia symptom severity more than cannabidiol (CBD) strains and sativa-dominant strains. Among individuals managing insomnia symptoms in depression, indica-dominant, indica hybrid, and sativa-dominant strains were perceived to be more efficacious than CBD strains. An additional investigation of several mental health conditions revealed pre-symptom severity, age, gender, and the ratio of CBD to THC as the factors most strongly associated with symptom change following cannabis use. Distinct patterns of cannabis response were also observed between individuals with insomnia, depression, and anxiety.

Conclusion: Our research investigating cannabis use for insomnia symptom management suggests that across conditions, individuals may perceive symptom improvements with cannabis use. Our subsequent work on cannabis use for mental health suggests that symptom profiles may have a role in the perceived effects of cannabis. These results highlight the therapeutic potential of cannabis-based products for sleep and mental health; however, the generalizability of this work is limited due to potentially biased samples of cannabis users who may have been more likely to perceive cannabis as effective. Our findings further emphasize the need for placebo-controlled investigations that can assess the safety and efficacy of cannabinoid treatments for general therapeutic use.

Keywords

therapeutic cannabis, mental health, sleep, symptom management, insomnia, depression, anxiety

Dedicated to my father, Nila Kuhathasan (1958-1997),

who shared his wisdom and love for me through the words that he wrote,

and to my dearest friend, Meruba Sivaselvachandran (1997-2021),

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List of Abbreviations

AHI	Apnea Hypopnea Index
ALS	Amyotrophic lateral sclerosis
CAPS	Clinician-Administered PTSD Scale
CBD	Cannabidiol
CBT-I	Cognitive Behavioral Therapy for Insomnia
CONSORT	Consolidated Standards of Reporting Trials
eCB	Endocannabinoid
ECS	Endocannabinoid System
EEG	Electroencephalogram
EMA	Ecological momentary assessment
ESS	Epworth Sleepiness Scale
FDA	United States Food and Drug Administration
GABA	Gamma-aminobutyric acid
GAD	Generalized anxiety disorder
GBD	Global Burden of Disease
HIPA	Health Information Protection Act
ISI	Insomnia Severity Index
LMEM	Linear mixed effects modeling
LSEQ	Leeds Sleep Evaluation Questionnaire
MAE	Mean absolute error
MDD	Major depressive disorder
MDE	Major depressive episode
MMAR	Marihuana Medical Access Regulations
MMPR	Marihuana for Medical Purposes Regulations
MOSSS	Medical Outcomes Study Sleep Scale
MS	Multiple sclerosis
NES	Nightmare Effects Survey
NFQ	Nightmare Frequency Questionnaire
NREM	Non-rapid eye movement
NRS	Numerical Rating Scale
OSA	Obstructive sleep apnea
PSQI	Pittsburgh Sleep Quality Index
PTSD	Posttraumatic stress disorder
RA	Rheumatoid arthritis
RCT	Randomized controlled trial
REM	Rapid eye movement
SD	Standard Deviation
SHAP	SHapley Additive exPlanations
THC	Tetrahydrocannabinol

Declaration of Academic Achievement

Chapter 2

N. Kuhathasan contributed to the study design, performed the literature search and data extraction, assessed articles for risk of bias, and composed the final manuscript. A. Dufort contributed to the study design, assisted with the literature search and data extraction, assessed articles for risk of bias, aided with the composition of the manuscript, and provided critical revision of the final manuscript. J. MacKillop, R. Gottschalk, and L. Minuzzi, provided critical revision of the manuscript. B.N. Frey contributed to the study design, assessed select articles for risk of bias, and provided critical revision of the manuscript.

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Chapter 3

N. Kuhathasan contributed to the study design, performed statistical analyses, and composed the final manuscript. L. Minuzzi contributed to the study design and data analysis plan, provided statistical guidance, and provided critical revision of the manuscript. J. MacKillop contributed to the study design, assisted with the interpretation of results, and provided critical revision of the manuscript. B.N. Frey contributed to the study design and data analysis plan and provided critical revision of the manuscript.

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Chapter 1: Introduction

1.1 Overview of Therapeutic Cannabis for Mental Health

Over two decades have passed since the legalization of medical cannabis in Canada. With the rising popularity of recreational cannabis, its therapeutic use has become increasingly common. Mental health concerns are frequently reported among the leading reasons for therapeutic use, though they are often understudied in this context (Walsh et al., 2013; Sexton et al., 2016; Piper et al., 2017; Kosiba et al., 2019). In fact, a 2013 study investigating therapeutic cannabis use in a Canadian sample, found that individuals who reported depression and anxiety as primary reasons for cannabis use were less likely to have received federal authorization to access the drug (Walsh et al., 2013). The researchers noted that the finding may have reflected the restricted access to medical cannabis at the time, and the absence of these disorders in the list of federally approved conditions. The ambiguity of whether depression and anxiety could qualify for medical cannabis authorization may have also highlighted the stigma associated with cannabis use for mental health. Despite this, insomnia, depression, and anxiety are among the top reasons for therapeutic use and are often cited as the most common mental health symptoms managed with cannabis (Piper et al., 2017; Kosiba et al., 2019; Lowe et al., 2019). This emphasizes the need for additional research on how cannabis is being used for mental health, while presenting a unique avenue of exploration for novel approaches toward the treatment of these conditions.

1.2 Cannabis Legalization in Canada

Because of its reported therapeutic properties, cannabis is often sought-after for medical purposes. In Canada, the cannabis market has rapidly evolved since medical and recreational cannabis were first legalized. Medical cannabis was legalized in Canada under the first iteration of the 2001 Marihuana Medical Access Regulations (MMAR). In the years that followed, the MMAR underwent several revisions to improve access, leading the federal government to relaunch the program as the Marihuana for Medical Purposes Regulations (MMPR) in 2013. Under the revised regulations, the process of authorizing access to medical cannabis was transferred to eligible healthcare professionals, with nearly any condition qualifying for medical cannabis use. In addition, the federal government also required all medical cannabis products to be obtained from government-approved licensed producers, marking the beginning of a federally regulated commercial cannabis market (Fischer et al., 2020; Turna et al., 2020).

A marked increase in cannabis use was observed among Canadians following the legalization of medical cannabis. The number of clients registered for medical cannabis use increased from approximately 8,000 in early 2014, to over 340,000 by September 2018 (Turna et al., 2020). By 2016, the federal government established the Task Force on Cannabis Legalization and Regulation, mandating consultations from Canadian community and stakeholder groups. Through the investigation, the task force was appointed to design a framework for legalization and regulation. In October 2018, the federal government formally implemented the Cannabis Act, providing all Canadians legal access to dried cannabis flower and oil. The following year, regulations for the

production and sale of cannabis-based edibles, extracts, and topicals were also finalized (Fischer et al., 2020; Turna et al., 2020; Lazor et al., 2022). While our understanding of cannabis use is limited, regulations around its access continue to rapidly develop. Research on its use has only recently gained traction, and there remains much to be explored.

1.2.1 Cannabis Legalization in Other Countries

Following Uruguay, Canada was the second country to legalize recreational cannabis at a federal level. While recreational cannabis remains illegal in most countries, medical cannabis is globally less restricted. Several countries have specific policies in place for medical cannabis, with acceptable usage varying by jurisdiction, indication, quantity accessed, and approving authority. In the US, cannabis is currently illegal under federal law; however, medical cannabis is legal in over half of all states with a doctor's recommendation (Bahji & Stephenson, 2019). While only a few states have currently legalized recreational use, the potential for therapeutic cannabis use has also led to many successful campaigns for legalization and decriminalization in other states (Martin, 2016). In the UK, medicinal products containing cannabinoids derived from cannabis plants are referred to as "cannabis-based products for medicinal use". These products are regulated as medical products and can be prescribed by specialists for therapeutic purposes (Freeman et al., 2019; National Institute for Health and Care Excellence [NICE], 2019). While the policy may seem to favour therapeutic cannabis use, these products exist under the larger umbrella of "medical cannabis" and have varying mechanisms of actions,

concentrations, and indications. Specialists must therefore consider each of these distinctions and note that indications are supported by valid evidence before prescribing medical cannabis (Freeman et al., 2019; NICE, 2019). Australia follows similar guidelines, with accessibility to medical cannabis products restricted to patients with prescriptions acquired through doctors or pharmacists. Despite this, medicinal cannabis remains classified as an unapproved medicine in the country (Department of Health and Aged Care Therapeutic Goods Administration, 2017). As regulatory frameworks around cannabis use develop at a global level, perceptions around therapeutic use continue to shift across countries. In turn, these perceptions may further influence how patients and health professionals seek and prescribe cannabis for therapeutic purposes.

1.3 Insomnia

Insomnia is a common sleep complaint characterized by dissatisfaction with sleep quantity or quality (American Psychiatric Association, 2013). It is often observed in both general and clinical populations and is present at both symptom and diagnostic levels (Morin & Benca, 2017). Insomnia can also present as either a separate or comorbid condition with other medical and psychiatric diagnoses (American Psychiatric Association, 2013; Morin & Benca, 2017). Nevertheless, independent of other conditions, insomnia can increase the risk of additional medical complications (Franzen & Buysse, 2017).

Beyond the general characteristics of insomnia described above, clinical presentations include significant distress and functional impairment resulting from sleep

difficulties. Furthermore, these sleep difficulties are often frequent (occurring at least 3 nights a week) and persistent (present for at least 3 months) (American Psychiatric Association, 2013). Approximately 30% of adults report symptoms of insomnia, while an estimated 10% of individuals report experiencing chronic insomnia (Bhaskar et al., 2016; Morin & Benca, 2017). Higher rates have been estimated in Canadians, with one study reporting 40.2% of adults presenting with at least 1 symptom of insomnia, and 13.4% meeting all criteria (Morin et al., 2011). The burden of persistent insomnia can also have substantial impacts on both individuals and society. In Canada, an estimated 80,000 working days are lost annually due to insufficient sleep (Chaput et al., 2022). In 2020, this amounted to a total of approximately $501.9 million in direct and indirect costs as a result of insufficient sleep alone (Chaput et al., 2022). At the individual level, insomnia is often associated with reduced quality of life, decreased productivity, increased absenteeism, and decreased cognition and mood (Wade, 2011; Ishak et al., 2012; Chaput et al., 2022). Moreover, roughly 70% of individuals with initial symptoms of insomnia, continue to report these symptoms the following year (Morin & Benca, 2012). As such, the impact of the condition remains significant, and evidently, strategies for the management and treatment of insomnia remain a primary focus of sleep research.

1.4 Depression

Depressive disorders are mood disorders that are characterized by persistent low mood and/or loss of interest in pleasurable activities. Several types of depressive disorders have been categorized by the American Psychiatric Association; however,

common features across depressive disorders include feelings of sadness and emptiness, accompanied by additional somatic and cognitive changes that can significantly affect individual functioning (American Psychiatric Association, 2013). As depressed mood is a common symptom of many psychiatric conditions, the context, presentation, and duration of symptoms are often considered at the time of diagnosis (First, 2013).

Among the most common depressive disorders is major depressive disorder (MDD), which is classified by episodes of depressed mood and/or anhedonia that persist for at least 2 weeks. These episodes must also include 5 or more other symptoms, including changes in weight or appetite, changes in sleep, psychomotor agitation, feelings of worthlessness or guilt, loss of energy, difficulties concentrating, and suicidal ideations (American Psychiatric Association, 2013). In addition, individuals with these symptoms often experience functional impairments and decreased quality of life (Xiao et al., 2018; Tanner et al., 2019). In Canada, the annual and lifetime prevalence of a major depressive episode (MDE) is 4.7% and 11.3%, respectively (Patten et al., 2015; Lam et al., 2016). The annual and lifetime prevalence of MDD, excluding bipolar disorders, is 3.9% and 9.9%, respectively (Patten et al., 2015; Lam et al., 2016). Globally, MDD is estimated to affect approximately 322 million people and is noted as the leading cause of disability worldwide (Vigo et al., 2022). In the 2019 Global Burden of Disease (GBD) study, the health burden of MDD was reported to account for an estimated 1.47% of all disability-adjusted-life-years, ranking among the top 25 leading causes of burden worldwide (Santomauro et al., 2021; Vigo et al., 2022). This immense health burden is also reflected in economic costs and the use of healthcare resources. MDD is associated with factors,

such as absenteeism and low work performance, that have substantial impacts on workplace costs (Kessler, 2012). Across Canada, the economic burden of depression is over $12 billion per year (Eccles et al., 2021). Taken together, depression places a considerable burden at both individual and societal levels, further justifying the need for research investigating potential improvements to treatment and care.

1.5 Anxiety

Anxiety is a negative affective state that is characterized by cognitive and physiological responses to real or perceived future threats (American Psychiatric Association, 2013). Although anxiety is closely related to the emotional response of fear, the two phenomena should be differentiated because of their distinct psychological and physiological responses. Anxiety is future-oriented and manifests as a complex neuropsychological response in anticipation of a threat. In contrast, fear is an immediate emotional response to a threat, and is often associated with intense physiological symptoms (Roma & Hope, 2017).

Anxiety becomes pathological when it impacts functioning or causes significant distress and can be further classified into several distinct disorders. These anxiety disorders share the core feature of anxiety and can be distinguished between one another by their triggering stimuli and resulting responses (American Psychiatric Association, 2013; First, 2013). Anxiety disorders are also commonly associated with several physiological and behavioral symptoms including palpitations, increased heart rate, threat

avoidance, and agitation among many others (American Psychiatric Association, 2013; Roma & Hope, 2017; Hughes, 2017).

Anxiety is often reported as one of the most common mental health concerns. In Canada, the annual prevalence of generalized anxiety disorder (GAD) is 2.6%, while the lifetime prevalence is 8.7% (Watterson et al., 2017). According to findings from the Global Burden of Disease (GBD) study, an estimated 45.8 million people worldwide struggled with an anxiety disorder in 2019 (Yang et al., 2021; Xiong et al., 2022). In addition to its prevalence, anxiety is also ranked among the leading causes of burden (Santomauro et al., 2021, Yang et al., 2021; Xiong et al., 2022). Considered one of the two most disabling mental health concerns globally, anxiety disorders ranked as the second leading mental health-related cause of disability-adjusted-life-years and years lived with disability (Santomauro et al., 2021). Although the classification of distinct anxiety disorders can lead to difficulties estimating the exact burden of the condition, existing epidemiologic studies suggest that together, the prevalence and comorbidity of anxiety is strikingly high, posing a serious public health concern (Stein et al., 2017; Xiong et al., 2022).

1.6 Sleep and Psychiatric Disorders

Adequate sleep serves as a fundamental regulatory process that is essential for both physical and mental health. Sleep disturbances occur when the quality and/or quantity of sleep are significantly affected, such that wellbeing and optimal functioning are impacted. During sleep, the human body will alternate between two primary sleep

states, rapid eye movement (REM) and non-REM (NREM), in cycles averaging 90 minutes in duration (Moszczynski & Murray, 2012; Franzen & Buysse, 2017). NREM sleep can further be classified into three stages, with each progressive stage corresponding to deeper sleep (Franzen & Buysse, 2017). While research on the underlying mechanisms and functions of sleep are still evolving, sufficient sleep remains an essential component of body and brain homeostasis.

In humans, sleep is regulated by the interactions between circadian rhythms and homeostatic responses. These processes involve multiple regions and networks across the brain (Levenson et al., 2015; Franzen & Buysse, 2017). As such, it is thought that sleep may be implicated in several specific activities within the brain. A growing body of literature supports the theory, with original studies revealing the significance of sleep in memory consolidation (Maier & Nissen, 2017; Klinzing et al., 2019), emotional processing (Palmer & Alfano, 2017; Tempesta et al., 2018), neuroplasticity (Palagini et al., 2019; Nissen et al., 2021), and numerous other brain processes. As these processes are central to psychopathology, sleep disturbances that result in impaired brain functioning can have large contributions to psychiatric disorders and their clinical outcomes.

Indeed, sleep disturbances are commonly observed across individuals with primary psychiatric diagnoses, with approximately 50-80% of individuals reporting sleep disturbances at some point over the course of a psychiatric condition (Baglioni et al., 2016; Franzen & Buysse, 2017; Seow et al., 2018; Khurshid, 2018; Palagini et al., 2022). Too little or too fragmented sleep, two elements of insomnia, are the most reported of these disturbances (Franzen & Buysse, 2017). Though difficulties with sleep are frequent

in most mental health conditions, insomnia is particularly prevalent in individuals with mental disturbances. An estimated 70-80% of individuals in the acute phase of a mental disorder report experiencing insomnia, and it is often viewed as a transdiagnostic symptom for many of these conditions (Krystal, 2012; Khurshid, 2018; Palagini et al., 2022).

While sleep difficulties have traditionally been observed as symptoms of many psychiatric disorders, recent research suggests a more complex, bidirectional relationship at play. For instance, sleep disturbances have been shown to predict the onset of various mental health conditions, often serving as independent risk factors for psychiatric relapses and recurrences (Franzen & Buysse, 2017; Hombali et al., 2019; Palagini et al., 2022). Although treatments for psychiatric disorders do not always alleviate co-occurring sleep-related symptoms, many studies have reported positive effects on mental health symptom severity with interventions that target sleep outcomes (Riemann et al., 2015; Atwood, 2022). These findings demonstrate that sleep disturbances might be better understood as important comorbid concerns in the presentation of psychiatric disorders. Moreover, recognizing the intersection between sleep and mental health may have the potential to improve clinical treatments and outcomes for psychiatric conditions.

1.6.1 Sleep Disturbances in Depression

Several studies have reported high rates of sleep disturbances, particularly symptoms of insomnia, in patients with depression. In fact, it is estimated that 80-90% of individuals with major depressive disorder report experiencing insomnia symptoms at

some point over the course of their condition (Geoffroy et al., 2018; Palagini et al., 2019; Hombali et al., 2019). Insomnia or hypersomnia is also listed as a symptom of the condition (American Psychiatric Association, 2013). Importantly, comorbid insomnia is highly associated with poorer treatment response (Krystal, 2012; Seow et al., 2018; Atwood, 2022), and insomnia alone has been known to predict future relapses and occurrences of depression (Baglioni et al., 2011; Li et al., 2016; Hertenstein et al., 2019; Riemann et al., 2020). In fact, a meta-analysis of 34 studies, reported that in the presence of insomnia, the risk of developing depression increased more than two-fold (Li et al., 2016). As such, it is evident that there is a strong connection between sleep disturbances and depressive disorders.

Although mechanisms that may link sleep and mood are still being explored, it has been hypothesized that disruptions in sleep may increase allostatic load through the dysregulation of REM sleep (Franzen & Buysse, 2017; Palagini et al., 2019; Van Someren, 2021). Allostatic load is the cumulative effect of chronic stress on physical and mental health. Previous studies have reported that REM sleep disruptions have been shown to affect the integrity of several brain structures, including the hippocampus (Palagini et al., 2013; Fjell et al., 2019; Lenart-Bugla et al., 2022). Largely involved in learning and memory processes, the hippocampus is also a key regulator of the stress response (MacQueen & Frodl, 2011; Sheline et al., 2019; Lenart-Bugla et al., 2022). Impairment of the hippocampus can therefore lead to hippocampal-dependent cognitive deficits and dysregulation of the stress response (MacQueen & Frodl, 2011; Navarro-Sanchis et al., 2017; Sheline et al., 2019; Lenart-Bugla et al., 2022). In this way, disrupted

REM sleep can become a chronic stressor over time and may contribute to functional impairments such as mood regulation. Repeated exposure to chronic stress can also contribute to further sleep difficulties, demonstrating that sleep disturbances can be considered both a cause and result of stress. This may highlight a possible role of poor sleep in the pathogenesis of depression and other mental health conditions (Riemann et al., 2015; Franzen & Buysse, 2017; Van Someren, 2021; Palagini et al., 2022). Ultimately, disruptions in sleep have profound effects on various processes within the brain, and as follows, treatments targeting sleep disturbances may also improve mood. Ideal treatments for depression may act on several biological systems through some aspect of homeostatic regulation.

1.6.2 Sleep Disturbances in Anxiety

Sleep disturbances, especially insomnia, are quite prevalent in anxiety disorders. Indeed, some studies have reported rates of insomnia to be as high as 70-90% in individuals with anxiety disorders (Soehner & Harvey, 2012, Palagini et al., 2022). As is the case with depression, comorbid insomnia is largely associated with low treatment response in anxiety, while insomnia on its own, has been shown to predict the onset of future anxiety (Soehner & Harvey, 2012; Hertenstein et al., 2019; Chellappa & Aeschbach, 2022).

The link between anxiety and insomnia can be observed at a very fundamental level. At its core, anxiety is a state of hyperarousal in response to a perceived threat, and insomnia is thought to be a disorder of hyperarousal (Levenson et al., 2015; Kalmbach et

al., 2018). Despite this, it remains unclear whether hyperarousal is contributing to, or resulting from, these conditions. From a neurobiological standpoint, several studies have attempted to elucidate the underlying mechanisms behind the disorders by examining sleep and anxiety with respect to their shared networks in the brain (Franzen & Buysse, 2017; Gong et al., 2019; Palagini et al., 2022). Of note, increased activation of the amygdala has been demonstrated in both insomnia and anxiety. The amygdala is a region of the brain associated with emotion generation that actively contributes to fear circuits through the regulation of behavioural and physiological responses (Kim et al., 2011; Palagini et al., 2019; Gong et al., 2019; Šimić et al., 2021). As such, its impairment can trigger hyperactivity that can give rise to anxiety through further dysfunctions in the stress response (Kim et al., 2011; Palagini et al., 2019; Šimić et al., 2021). While these findings suggest overlapping mechanisms in insomnia and anxiety, they also warrant additional research on the unique pathophysiology of the conditions.

1.7 Overview of the Endocannabinoid System

The endocannabinoid system (ECS) is a complex physiological system that serves an essential function in the regulation of various brain processes. In recent years, the ECS has drawn considerable attention as a possible therapeutic target for mental disorders, largely because of its neuromodulatory role in the central nervous system (Bhattacharyya et al., 2010; Alger, 2013). Comprised of enzymes, cannabinoid receptors, and their endogenous ligands (i.e., endocannabinoids), the ECS is an important contributor to brain functions such as sleep, mood, and cognitive performance (World Health Organization,

2016). By binding to cannabinoid receptors, endocannabinoids can regulate the activity of neurotransmitters that are involved in these physiological and psychological processes (Ruehle et al., 2012; Mechoulam & Parker, 2013). The most widely established cannabinoid receptors implicated in ECS activity are CB1 and CB2 receptors. Primarily expressed in the brain, the CB1 receptor is among the most abundant receptors found in the central nervous system (Bhattacharyya et al., 2010; Alger, 2013). CB1 receptors are particularly concentrated in the hippocampus, prefrontal cortex, hypothalamus, basal ganglia, cerebellum, and amygdala (Pazos et al., 2005; Kruk-Slomka et al., 2017; Graczyk et al., 2021). These brain regions are associated with processes such as memory, cognition, motor function, and emotional response. In contrast, CB2 receptors are primarily expressed peripherally, and though less understood, are thought to play a role in immune responses (Pazos et al., 2005; Mechoulam & Parker, 2013; Kruk-Slomka et al., 2017).

The homeostatic function of the ECS is largely attributed to the activation of CB1 receptors located across several synapses in the central nervous system. As retrograde messengers, endocannabinoids are recognized as important regulators of synaptic homeostasis (Lu & Mackie, 2016; Alger, 2013; Fernández-Ruiz et al., 2020). Endocannabinoids are synthesized as required and released through presynaptic inhibition. By binding to CB1 receptors, endocannabinoids inhibit the release of GABA and glutamate, thereby regulating the release of other neurotransmitters including dopamine, serotonin, acetylcholine, histamine, and norepinephrine (Mechoulam & Parker, 2013; Lu & Mackie, 2016; Fernández-Ruiz et al., 2020). In this way, the

activation of CB1 receptors maintains synaptic homeostasis through the regulation of excitatory and inhibitory neuronal activity.

Cannabis contains several exogenous cannabinoids that can also act as ligands for cannabinoid receptors. To date, over 100 distinct plant-derived cannabinoids (or phytocannabinoids) have been identified (Bhattacharyya et al., 2010; Alger, 2013; Sarris et al., 2020). Cannabis also has hundreds of distinct chemical compositions (or chemovars), with complex constituent profiles and associated effects (Alger, 2013; Sarris et al., 2020). The two major phytocannabinoids found in cannabis are delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD). THC, the main psychoactive component of the drug, is a partial agonist of CB1 and CB2 receptors; however, it primarily exerts its psychoactive effects by activating CB1 receptors in the brain (Alger, 2013; Navarrete et al., 2020; Laksmidewi & Soejitno, 2021). Recent research has also proposed that the euphoric effects often associated with THC may be explained by increases in dopamine production following consumption. Interestingly, the same dopaminergic effect is not observed following chronic THC consumption, with research instead reporting blunted dopamine synthesis and release (Hernandez & Cheer, 2015; Bloomfield et al., 2016; Laksmidewi & Soejitno, 2021). The precise mechanisms that may be responsible for these effects are still under investigation. In contrast, CBD is the major non-psychoactive component of cannabis. Some evidence suggests that it may function as a negative allosteric modulator of the CB1 receptor by binding to a different site from that of THC (Navarrete et al., 2020; Graczyk et al., 2021). It is of particular interest as a therapeutic target, as it is thought to balance the effects of THC to deliver

therapeutic responses with reduced adverse reactions (Navarrete et al., 2020; Sarris et al., 2020; Graczyk et al., 2021).

The modulatory role of the ECS in the brain illustrates how the system is connected to many other neurobiological processes. Its function also demonstrates potential modes of action for the ECS to be implicated in various neuropsychiatric disorders. Some research even suggests that malfunctions in specific components of the ECS may contribute to the pathophysiology of these disorders (Mechoulam & Parker, 2013, Navarrete et al., 2020; Fernández-Ruiz et al., 2020). As such, pharmacological manipulation of the ECS may serve as a promising therapeutic target for these psychiatric disorders and their related symptoms.

1.8 Understanding Cannabis Use for Sleep and Mental Health

Rates of cannabis use in Canada have increased substantially since legalization. It is one of the most widely used substances in the country and nearly half of all Canadians have reported trying it (Rotermann, 2019). As federal policies around the access, production, and sale of cannabis continue to evolve, interest in understanding both motives for cannabis use and the patterns of use have become an important public health priority. Investigating its use for mental health is of particular importance, as these conditions are often reported among the top therapeutic reasons for use (Walsh et al., 2013; Sexton et al., 2016; Piper et al., 2017; Kosiba et al., 2019). The overarching goal of our research was to explore how Canadians used cannabis to manage sleep and mental health concerns. As such, we broadly examined data collected from large naturalistic

samples of cannabis users. We began by conducting a critical review of available clinical studies on cannabis and sleep. Next, we analyzed data collected from a mobile app that allows cannabis users to monitor their usage. These investigations primarily examined how individuals used cannabis to manage insomnia symptoms. We then explored the factors that contributed to perceived mental health symptom improvement following cannabis use.

1.8.1 Aims & Objectives

Our research specifically aimed to determine patterns and profiles of cannabis use that might inform public policy and future studies. The objectives of this work are as follows:

1. In chapter 2, we provide our brief review of literature that examined cannabinoid use for sleep, and critically assess relevant clinical trials that investigated the effects of cannabinoids on various sleep outcomes.
2. In chapters 3 and 4, we present two separate retrospective studies that analyzed data from large naturalistic samples to understand patterns and profiles of cannabis use for insomnia symptoms, both exclusively and within the conditions of depression or anxiety.
3. In chapter 5, we introduce a study that used machine learning methods to investigate predictors of symptom change in individuals who consumed cannabis for mental health management.

1.8.2 Hypotheses

Our hypotheses for the studies outlined above are as follows:

1. Previous research on recreational cannabis use has reported some benefits for sleep, so we expected to find several studies highlighting the positive therapeutic effects of cannabis. We did, however, anticipate that clinical research would be limited.
2. Based on the results of our review, we predicted some general symptom improvements for insomnia with cannabis use. Findings from our review also revealed varying responses to specific product formulations, so we expected to observe differences in perceived symptom improvement between cannabis strain categories. In our follow-up study, we also predicted response differences between individuals with depression and anxiety. Our work in these domains was largely exploratory, as a lack of previous research made it unclear how responses could vary.
3. We had observed some differences between strain categories in our other studies, so we expected that the composition of cannabis products would be a top predictor of symptom change. As previous research has reported that baseline symptom severity can influence clinical outcomes, we also expected pre-symptom severity to be a key predictor. This study was also largely exploratory due to a lack of existing research in the field.

1.9 References

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Chapter 2: The Use of Cannabinoids for Sleep: A Critical Review on Clinical Trials

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Abstract

Cannabis and its pharmacologically active constituents, phytocannabinoids, have long been reported to have multiple medicinal benefits. One association often reported by users is sedation and subjective improvements in sleep. To further examine this association, we conducted a critical review of clinical studies examining the effects of cannabinoids on subjective and objective measures of sleep. PubMED, Web of Science, and Google Scholar were searched using terms and synonyms related to cannabinoids and sleep. Articles chosen included randomized controlled trials and open label studies. The Cochrane risk of bias tool was used to assess the quality of trials that compared cannabinoids with control interventions. The current literature focuses mostly on the use of tetrahydrocannabinol (THC) and/or cannabidiol (CBD) in the treatment of chronic health conditions such as multiple sclerosis, posttraumatic stress disorder (PTSD), and chronic pain. Sleep is often a secondary, rather than primary outcome in these studies. Many of the reviewed studies suggested that cannabinoids could improve sleep quality, decrease sleep disturbances, and decrease sleep onset latency. While many of the studies did show a positive effect on sleep, there are many limiting factors such as small sample sizes, examining sleep as a secondary outcome in the context of another illness, and relatively few studies using validated subjective or objective measurements. This review also identified several questions that should be addressed in future research. These questions include further elucidation of the dichotomy between the effects of THC and CBD, as well as identifying any long-term adverse effects of medicinal cannabinoid use.

Public Health Significance

This review characterizes the clinical research that suggests that cannabinoids may favorably impact sleep disturbance, with study participants often reporting a subjective improvement in their sleep quality. However, objective data is lacking, and clinical ramifications remain unclear. Given the prevalence and impact of sleep disorders, further research is warranted to identify whether or not cannabinoids could be used as an effective clinical agent.

Keywords

cannabis, sleep, THC, CBD, insomnia

2.1 Introduction

Cannabis is the most widely used illicit substance in the U.S. with national data from 2014 indicating that 9.5% of adults reported use within the preceding year (Hasin et al., 2015). While recreational use remains illegal in most states, nine states and Washington, DC now have legislation which allows for everyday use. This is in addition to national legalization in Canada, where rates of cannabis use are higher than the U.S. (past year prevalence = 12.5%; CTADS, 2015). Among Canadian students, cannabis use generally remains unchanged, with 17% of students in Grades 7 to 12 reporting cannabis use in the preceding year (CSTADS, 2017). This places cannabis use as the next highest prevalence of use after alcohol in Canadian students (CSTADS, 2017). In addition to its recreational use, cannabis has a history of medicinal use dating back to 400 AD (Zias et al., 1993). In fact, cannabis was listed in the United States Pharmacopoeia up until 1942 (Bridgeman & Abazia, 2017). From that point, legal use and research into medicinal cannabis has laid mostly dormant. That was until 1996 when California became the first state enacting legalization permitting medicinal use (Bridgeman & Abazia, 2017). Currently, medical marijuana, along with herbal extracts and several synthetic preparations are used therapeutically throughout North America.

As the use of cannabis for medicinal and therapeutic purposes has increased, so has research into this field. Empirically, evidence of varying quality exists for the use of cannabinoids in the treatment of spasticity related to multiple sclerosis, nausea, chronic pain, epilepsy, and anorexia associated with AIDS (Volkow, Baler, Compton, & Weiss, 2014; Whiting et al., 2015). While legal in many states, medicinal use of cannabis is not

approved by the FDA for any indications. Epidiolex, a purified, CBD concentrated extract of cannabis has recently been approved to treat seizures associated with Lennox-Gastaut syndrome and Dravet syndrome. Recreational and medicinal users of cannabis also report a wide array of self-perceived benefits and reasons for cannabis use (Azofeifa et al., 2016; Lee, Neighbors, & Woods, 2007; Walsh et al., 2013). One benefit that is commonly reported is that cannabis use aids with sleep (Walsh et al., 2013). In one study, approximately one fourth of recreational users reported using cannabis to help them relax and achieve sleep (Lee et al., 2007). This possible therapeutic benefit could be quite substantial given the widespread impact of insomnia and sleep disorders. From an epidemiological point of view, it is estimated that approximately 10% of adults suffer from chronic insomnia. In addition, one third of adults are estimated to suffer from occasional or intermittent insomnia symptoms on an annual basis (Ferrie, Kumari, Salo, Singh-Manoux, & Kivimäki, 2011). Insomnia and other sleep disorders are estimated to cost the American economy billions of dollars either directly through health care costs or indirectly through loss of productivity and accidents (Hossain & Shapiro, 2002). Given all of the above, the possible benefits of cannabis use on sleep may provide a new therapeutic avenue to individuals suffering from insomnia and sleep disorders.

The goal of this article is to provide a critical review of the data from trials examining the effects of various cannabinoid preparations on sleep, dichotomizing the results by the types of cannabinoid preparation and the study populations. From a clinical perspective, studies dating back to the 1970s have examined the clinical effects of cannabinoid administration on sleep in various patient populations. We focused on

clinical trials that used a wide variety of measurements ranging from subjective scales, validated scales, and objective measurements. Then, we integrated the data into what is known about the management of sleep disorders and discuss whether or not some of these cannabinoids may have a potential clinical role. Basic research on the interplay between the endocannabinoid system and sleep physiology is intriguing and has been reviewed extensively elsewhere (Prospéro-García, Amancio-Belmont, Becerril Meléndez, Ruiz-Contreras, & Méndez-Díaz, 2016). Lastly, we propose areas of future research.

2.2 Method

A literature review was performed by searching PubMed, Web of Science, and Google Scholar using appropriate key words and synonyms related to cannabis, cannabinoids, sleep, and insomnia. The specific search strategy keywords included "sleep or insomnia or sleep quality or sleep architecture or sleep study or sleep disorder or sleep treatment" and "cannabis or cannabinoids or marijuana or nabiximols or sativex or cesamet or nabilone or CBD or THC or cannabidiol or tetrahydrocannabinol." Selected articles included randomized control trials and open label studies that focused on the effects of cannabinoids on sleep, either as a primary or secondary outcome (see Table 1). The reference lists of both review and original research articles were examined to identify further references that would be applicable to the goals of this paper. Articles were chosen in a way to provide a summary of the highest quality evidence in a balanced and unbiased manner. Further, the quality of individual studies that compared cannabinoid interventions versus control interventions was assessed using the Cochrane Risk of Bias

Tool (Higgins & Green, 2011: see Table 2). Three independent reviewers (N.K., A.D., B.F.) assessed the risk of bias and discrepancies were resolved through face-to-face discussion. Despite these safeguards, a limitation of this article is that it is not a systematic review of the literature.

2.3 CBD, THC, and Pharmaceutical Formulations

Despite its widespread use and lengthy history of human consumption, the biochemical properties and pharmacological effects of cannabis are still being fully elucidated. At the moment, the cannabis plant is thought to be made up of more than 500 chemical compounds, 104 of them being defined phytocannabinoids (Lafaye, Karila, Blecha, & Benyamina, 2017). The two phytocannabinoids that have been the best characterized in regards to their pharmacological effects and potential uses in treating sleep disorders are: Δ9-tetrahydrocannabinol (Δ9-THC) and cannabidiol (CBD). The effects of these two phytocannabinoids are modulated through CB1 and CB2 receptors (Pertwee, 2008). These particular receptors are part of the human endocannabinoid system and can recognize endogenous compounds similar in structure to endocannabinoids (Murillo-Rodríguez et al., 2018). The resulting effects of these phytocannabinoids are often similar to those produced by endocannabinoids (Murillo-Rodríguez et al., 2018). Broadly, THC is responsible for the psychoactive properties of cannabis as well as many of the cognitive and behavioral adverse effects. THC concentrations can vary by cannabis plant and preparation and with it the potency of the drug (Lafaye et al., 2017). CBD was originally thought to be physiologically inactive;

however, various studies have now shown that CBD may antagonize the action of THC and may mitigate some of the adverse effects such as psychosis and anxiety (Niesink & van Laar, 2013). As the human endocannabinoid system has been characterized, several human and animal studies have also identified an association between this system and the sleep wake cycle. This association includes the observation that levels of multiple endocannabinoids and CB1 vary throughout the sleep wake cycle and are under circadian control (Prospéro-García, Amancio-Belmont, Becerril Meléndez, Ruiz-Contreras, & Méndez-Diaz, 2016). In addition, multiple endocannabinoids have been shown to promote both REM and NREM sleep through various pathways and brain structures (Prospéro-García et al., 2016).

Traditionally, phytocannabinoids have exerted their pharmacological effects through combustion and inhalation of the plant or through ingestion of edible preparations (Russo, 2007). With the advent of research into the medicinal properties of phytocannabinoids, several pharmaceutical preparations have been created. The three preparations relevant for this review are nabiximols (marketed as Sativex, not approved by the FDA, approved by Health Canada for the treatment of refractory spasticity and neuropathic pain in patients suffering from multiple sclerosis as well as refractory pain associated with cancer), nabilone (marketed as Cesamet, approved by the FDA for the treatment of refractory nausea and vomiting associated with cancer chemotherapy), and dronabinol (marketed as Marinol, approved by the FDA for the treatment of anorexia associated with AIDS as well as refractory nausea and vomiting associated with cancer chemotherapy). Dronabinol is a synthetic delta-9-THC, with doses ranging from 2.5–10

mg. Nabilone is a synthetic cannabinoid, with doses ranging from 0.5–1 mg. Nabiximols is a cannabis plant extract that is delivered through an oromucosal spray, which delivers 2.7 mg of THC and 2.5 mg of CBD per spray.

2.4 Clinical Studies

2.4.1 Sleep and THC Derivatives

A total of 18 studies investigated the effects of THC treatments on sleep (Beaulieu, 2006; Bedi et al., 2010; Bestard & Toth, 2011; Brisbois et al., 2011; Cameron, Watson, & Robinson, 2014; Carley et al., 2018; Côté, Trudel, Wang, & Fortin, 2016; Farabi, Prasad, Quinn, & Carley, 2014; Frank, Serpell, Hughes, Matthews, & Kapur, 2008; Fraser, 2009; Gorelick et al., 2013; Jetly, Heber, Fraser, & Boisvert, 2015; Narang et al., 2008; Prasad, Radulovacki, & Carley, 2013; Roitman, Mechoulam, Cooper-Kazaz, & Shalev, 2014; Toth et al., 2012; Ware, Fitzcharles, Joseph, & Shir, 2010a; Weber, Goldman, & Truniger, 2010). These studies used the synthetic equivalents of THC, nabilone, and dronabinol, to treat patients with various ailments. Of note, sleep was primarily observed as a secondary outcome. Despite this limitation, the majority of the studies reported that THC analogue use improved subjective sleep quality (Bedi et al., 2010; Bestard & Toth, 2011; Brisbois et al., 2011; Cameron et al., 2014; Farabi et al., 2014; Fraser, 2009; Gorelick et al., 2013; Jetly et al., 2015; Narang et al., 2008; Prasad et al., 2013; Roitman et al., 2014; Toth et al., 2012; Ware et al., 2010a). Seven of these studies also reported subjective decreases in sleep disturbances and in nightmare frequency (Bedi et al., 2010; Cameron et al., 2014; Fraser, 2009; Jetly et al., 2015;

Narang et al., 2008; Roitman et al., 2014; Toth et al., 2012). These studies are discussed in more detail below.

In addition to these studies, a number of experiments were also performed in the 1970s–1980s that examined the effects of cannabinoids on sleep through use of objective measurements. First, Hosko, Kochar, and Wang (1973) assessed the effects on sleep of two doses of oral THC (200 mg/kg and 300 mg/kg) via electroencephalogram (EEG) in seven males with varying history of prestudy cannabis use. This study demonstrated inconsistent effects on slow wave sleep and REM sleep time. The data was also limited by the heterogeneity of the study population, ranging from naïve to heavy users of cannabis. A similar study was performed by Tassinari, Ambrosetto, Peraita-Adrados, and Gastaut (1976) where nine drug naïve individuals were given oral THC (0.7–1.4 mg/kg) and the effects on sleep were measured by EEG. They identified consistent increases in Stage 2 sleep and decreases in slow wave and REM sleep. Lastly, Pivik, Zarcone, Dement, and Hollister (1972) treated four young males with oral THC (61 to 258 μg/kg) just prior to sleep. Overnight EEG recordings identified increased Stage 4 sleep and decreased REM sleep in all subjects. Higher doses were associated with decreased time spent awake after sleep and decreased Stage 1 sleep.

2.4.1.1 THC for PTSD: Findings Relating to Sleep

Individuals suffering from posttraumatic stress disorder (PTSD) experience both emotional and behavioral symptoms as a result of previous traumatic events (Jovanovic & Norrholm, 2011). PTSD is often associated with nightmares and poor sleep quality

(Jovanovic & Norrholm, 2011). In recent years, cannabinoids have been examined as a potential therapeutic avenue for the treatment of PTSD. One such randomized placebo-controlled trial treating PTSD-associated nightmares in military personnel found that titrated doses of nabilone, ranging from 0.5 mg to 3.0 mg over 7 weeks, promoted significant improvements in the Clinician-Administered PTSD Scale (CAPS) Recurring and Distressing Dream scores (Jetly et al., 2015). This study included patients with a history of nonresponse to standard treatments and demonstrated significant relief in 70% of subjects following THC treatments. In contrast, only 22% of subjects showed improvement following placebo treatments. Similarly, an open-label trial by Roitman, Mechoulam, Cooper-Kazaz, and Shalev (2014) examined patients on stable medication for chronic PTSD. Patients received 5 mg of THC dissolved in olive oil (concentrate 5 mg/0.2 cc) twice a day as an add-on therapy. Using validated measures of sleep quality, such as the Pittsburgh Sleep Quality Index (PSQI), the Nightmare Frequency Questionnaire (NFQ), and the Nightmare Effects Survey (NES), adjunctive THC significantly improved subjective measures of both sleep quality and frequency of nightmares with THC treatments. Fraser (2009) reported similar findings in an open label clinical trial of PTSD patients with treatment resistant nightmares. Patients in the randomized trial received titrated doses of nabilone ranging from 0.5–6 mg at bedtime. There was a subjective improvement in nightmare intensity, sleep quality, and sleep time in 72% of the patients receiving nabilone, with 59% experiencing total cessation of nightmares. Despite these findings, it is unclear as to whether the effect could be related

to REM sleep suppression. As the discussed studies did not examine this, future studies are encouraged to measure the potential side effect.

2.4.1.2 THC for Chronic Pain: Findings Relating to Sleep

Chronic pain is a severe symptom of many disorders and can be both physically and psychologically taxing. The persistent pain can also often interfere with an individual's quality of sleep (Burns & Ineck, 2006). Researchers have examined the effects of THC on chronic pain and sleep as a secondary outcome. A 2008 study by Narang et al. (2008) examined dronabinol as an adjuvant treatment for patients taking opioids for chronic pain. The study had two phases, with Phase 1 consisting of a randomized, double-blind, placebo-controlled crossover trial, and Phase 2 consisting of an open-label titrated trial. In Phase 1, patients were administered either 10 mg or 20 mg of dronabinol or a placebo over the course of three 8-hr visits. In Phase 2, patients receiving stable doses of opioids were administered titrated doses of dronabinol between 5 mg and 60 mg. Results indicated a subjective decrease of pain interference during sleep, as well as an overall subjective decrease in sleep disturbances. Another notable study examined patients with chronic neuropathic pain during a 14-week crossover trial administering dihydrocodeine or nabilone (Frank et al., 2008). Patients received a maximum daily dose of either 240 mg of dihydrocodeine or 2 mg of nabilone at the end of a 6-week escalating treatment period. The study examined self-reported measures of both pain and sleep quality and concluded that nabilone provided a weaker analgesic effect with no significant effect on sleep compared with dihydrocodeine. Similarly, a

study by Weber et al. (2010), examined 27 patients with amyotrophic lateral sclerosis (ALS) with moderate to severe muscle cramping. Patients were randomly assigned to receive 5 mg of dronabinol or placebo twice a day for 2 weeks before switching conditions after a 2-week washout period. Pain and quality of sleep were measured. Results demonstrated no subjective change in sleep following dronabinol treatment when compared to placebo. In contrast, Toth et al. (2012) reported an improvement in subjective measures of overall sleep and less sleep disruption, as measured by self-reports, with nabilone treatments versus placebo in individuals with diabetes-related neuropathic pain. Subjects were assessed for pain and sleep quality and were administered single-blinded adjuvant nabilone for 4 weeks. Patients achieving greater than 30% pain relief were then randomized and treated with a flexible nabilone dose (ranging from 1–4 mg/day) or placebo. Sleep index scores showed an improvement in overall sleep at Weeks 2, 4, and 5 and less sleep disruption at Weeks 6, 8, and 9. Overall, research on THC for chronic pain and sleep is limited and presents mixed results on the effects of this particular preparation of cannabis treatment for chronic pain.

THC has also been studied extensively alongside other drugs. One study investigated patients with chronic insomnia and a comorbid diagnosis of fibromyalgia (Ware et al., 2010a). In this study, THC was compared with amitriptyline, a sedative tricyclic antidepressant often used in the treatment of pain and depression. Patients were administered 0.5–1 mg of nabilone or 10–20 mg of amitriptyline in a cross-over design. Each treatment condition had a duration of 2 weeks, followed by a 2-week washout period before the subsequent condition. Validated scales such as the Insomnia Severity

Index (ISI) and the Leeds Sleep Evaluation Questionnaire (LSEQ) measured sleep quality. Despite both drugs having positive effects on sleep, nabilone was superior to amitriptyline. In a similar study, Bestard & Toth (2011) compared nabilone with gabapentin in patients suffering from neuropathic pain. The Medical Outcomes Study Sleep Scale (MOSSS) was used to measure sleep quality across various domains of sleep. Patients received a flexible daily dose of self-administered nabilone capsules (1–3 mg) in addition to gabapentin and were given the option to take the drugs together or as monotherapy. Sleep adequacy and sleep problem indices within the MOSSS improved in both nabilone monotherapy and in the adjuvant group. No significant sleep improvement was noted in the gabapentin group. While the overall effects of THC for pain-associated sleep disturbances are generally quite positive, it is important to note that many of these studies reported on select individuals who demonstrated greater pain relief with THC treatments or reported on the effects of THC treatments in tandem with other pain-relief medications.

2.4.1.3 THC for Obstructive Sleep Apnea: Findings on Sleepiness and Apnea/Hypopnea

In a recent randomized clinical trial investigating severe obstructive sleep apnea (OSA), self-reported Epworth Sleepiness Scale (ESS) scores were reduced significantly with high doses of dronabinol from baseline scores (−3.8 ± 0.8) and from placebo comparison scores (−2.3 ± 1.2; Carley et al., 2018). Patients in this study received either a placebo, 2.5 mg of dronabinol, or 10 mg of dronabinol daily, for up to 6 weeks. In comparison with placebo, patients receiving high doses of dronabinol reported greater

overall satisfaction regarding the treatment. In addition, individuals receiving high doses of dronabinol demonstrated dose-dependent improvements in sleepiness. Similarly, another study observing OSA patients reported significant improvements in the Stanford Sleepiness Scale (Prasad et al., 2013). Patients in this study received dronabinol starting at 2.5 mg daily, with doses increased weekly, to 5 mg, and 10 mg, as tolerated. The study reported significant changes from baseline in the Apnea Hypopnea Index (AHI), with no change in REM sleep or arousal. Though these results are promising, it is important to note that this particular study was a proof-of-concept study. To increase the reliability of these findings, further investigation is still needed. Overall, results from these studies support the notion of the potential medicinal benefits of dronabinol for the treatment of OSA.

2.4.1.4 THC for HIV-Related Disorders: Findings Relating to Sleep

A study by Bedi et al. (2010) examined HIV-positive subjects who smoked marijuana 4.2 ± 2.3 days per week. Subjects attended two laboratory sessions, 16 days each, and received 10 mg of dronabinol in one and a placebo in the other. Measured sleep outcomes included sleep latency, number of awakenings and sleep efficiency. Visual analogue scales were also used to measure subjective sleep quality. Results found that dronabinol improved transient sleep for the first eight nights of sleep. No such improvement was found between Days 9–16. Because the study was conducted in chronic marijuana smokers, it is possible that tolerance effects may have played a role in these results. Objectively, researchers reported increased NREM sleep, and decreased minutes

awake, as measured by a Nightcap sleep monitor. Subjective measures also suggested increased quality of sleep and decreased awakenings.

2.4.2 Sleep and Nabiximols (1:1 CBD:THC)

A total of nine studies investigated the effects of nabiximols as a treatment outcome for sleep (Blake et al., 2006; Collin et al., 2010; Langford et al., 2013; Novotna et al., 2011; Nurmikko et al., 2007; Portenoy et al., 2012; Rog et al., 2005; Serpell et al., 2014; Wade et al., 2004). These studies examined a range of 58–339 patients suffering from either chronic pain or multiple sclerosis. All of these studies were randomized, placebo-controlled trials, ranging from 4 to 14 weeks, and examined sleep as a secondary outcome. Across trials, doses ranged from eight to 12 sprays of 2.7 mg of THC and 2.5 mg of CBD. Unfortunately, most studies used visual analogue scales and none of the studies employed a validated sleep measure or employed objective techniques. Five of nine studies noted improvements in subjective sleep quality with varying doses of nabiximols (Blake et al., 2006; Collin et al., 2010; Langford et al., 2013; Serpell et al., 2014; Wade et al., 2004), and four studies reported improvements in subjective sleep disturbance-related scores (Novotna et al., 2011; Nurmikko et al., 2007; Portenoy et al., 2012; Wade et al., 2004). Despite the positive findings, three studies reported these results in relation to specific subgroups (i.e., patients in randomized withdrawal phases, patients with >30% of improvement in spasticity, and patients in low-dose groups), with no significant effect on the overall sample (Collin et al., 2010; Langford et al., 2013; Portenoy et al., 2012). Though the majority of these studies used non-validated,

subjective measures to examine secondary sleep outcomes, results indicated significant improvements in sleep quality and overall sleep. The following sections will describe these studies in further detail.

2.4.2.1 Nabiximols for Multiple Sclerosis and Spasticity

One of the foci for nabiximols has been in the treatment of multiple sclerosis (MS) related symptoms. Individuals suffering from MS often report spasticity as a major symptom of the disorder. Associated with severe spasms, the condition can be extremely debilitating for patients and can have a significant effect on sleep quality (Grandner & Pack, 2011). In recent years, cannabis has played a therapeutic role in the management of spasticity symptoms (Grandner & Pack, 2011). Studies suggest that nabiximols may have an effect on muscle relaxation, as the particular preparation acts as a partial agonist on cannabinoid receptors, playing a role in modulation between excitatory and inhibitory neurotransmitters (Russo et al., 2015). A review of clinical trials administering nabiximols for the management of MS symptoms demonstrated improvements in subjective spasticity as reported by patients undergoing treatments (Collin et al., 2010; Langford et al., 2013; Novotna et al., 2011; Wade et al., 2004). In one study, 337 MS patients with spasticity received a titrated dose of nabiximols over a 14-week treatment period (Collin et al., 2010). Patients then rated spasticity and sleep quality following the treatment using the spasticity numerical rating scale (NRS). Results from the study demonstrated no overall significant effect on self-reported sleep; however, patients with greater than 30% improvement in spasticity also reported a significant

improvement in sleep. In another study by Novotna et al. (2011), patients with MS and spasticity who were responsive to nabiximols were enrolled in a double-blind study examining the effect of a nabiximols treatment over a 4-week period. Patients were limited to a maximum of 12 sprays in a 24-hr period and were able to self-titrate for the first 10 days of treatment. Subjective measures from patients demonstrated an increase in sleep quality resulting from the treatment. Two additional studies reported improvements in sleep quality; however, these improvements were only noted in subgroups of patients undergoing a randomized withdrawal phase or who demonstrated >30% improvement in spasticity, respectively (Langford et al., 2013; Wade et al., 2004). Though these studies report promising improvements in sleep quality, it is important to note that more research is needed, as positive effects were likely a function of improvement in spasticity.

2.4.2.2 Nabiximols for Chronic Pain

Five of the present studies examined the effect of nabiximols treatment in patients suffering from some form of chronic pain (Blake et al., 2006; Nurmikko et al., 2007; Portenoy et al., 2012; Rog et al., 2005; Serpell et al., 2014). These studies reported improvements in subjective measures of both sleep quality and sleep disturbances with administration of nabiximols. A study by Blake et al. (2006) examined the role of cannabinoids in the treatment of pain in individuals with rheumatoid arthritis (RA). Over the course of a 5-week treatment period, patients were administered either nabiximols or a placebo. Each spray delivered 2.7 mg of THC and 2.5 mg of CBD, with an increase of one spray every 2 days to a maximum of six sprays from the starting dose. Despite the use

of lower doses of nabiximols, this particular study reported positive treatment results in subjective data. Results from the trial demonstrated significant analgesic effects, as well as significant improvements in subjective sleep quality following nabiximols treatments. Similarly, a 2014 study by Serpell et al. (2014) reported improvements in self-reported sleep quality of patients with peripheral neuropathic pain. A sample of 246 patients with peripheral neuropathic pain were randomized to receive either nabiximols or a placebo and were able to self-titrate to a maximum of eight sprays over 3 hr or 24 sprays over 24 hr. Results indicated an improvement in sleep quality ($p < .007$) as per a 10-point NRS. Although these studies predominantly observed sleep as a secondary outcome, all five studies reported that nabiximols doses improved overall sleep conditions; however, it is important to note that improvement in pain may have been a mediating factor.

2.4.3 Sleep and Other Cannabis Preparations

An additional 14 studies examined the effect of various combinations of cannabinoid treatments, including smoked cannabis, on sleep quality, sleep disturbances, and sleep onset latency (Berman et al., 2004; Brady et al., 2004; Cousens & DiMascio, 1973; Haney et al., 2007; Hosko et al., 1973; Johnson et al., 2010; Nicholson et al., 2004; Pivik, Zarcone, Dement, & Hollister, 1972; Tassinari et al., 1976; Vaney et al., 2004; Wade et al., 2003; Ware et al., 2010b; Zajicek et al., 2003; Zajicek et al., 2012). Six of these studies reported favorable outcomes for cannabinoid treatments over placebo, with patients demonstrating significant improvements within these sleep domains (Berman et al., 2004; Brady et al., 2004; Cousens & DiMascio, 1973; Wade et al.,

2003; Zajicek et al., 2003; Zajicek et al., 2012). Two notable studies that included a validated sleep measurement found that patients reported decreased sleep onset latency with use of cannabinoid treatments (Nicholson et al., 2004; Ware et al., 2010b). A study by Ware et al. (2010b) examined 23 patients with neuropathic pain. Patients smoked 25 mg of one of four different cannabis strains with varying THC potencies (0%, 2.5%, 6% and 9.4%) for 5 days, followed by a 9-day washout period. Results demonstrated that patients smoking the 9.4% THC potency cannabis reported less difficulty falling asleep with fewer sleep disturbances as measured by the Leeds Sleep Evaluation Questionnaire. In a similar study examining healthy volunteers, Nicholson et al. (2004) examined four different treatments (placebo, 15 mg THC, 5 mg THC/CBD, and 15 mg THC/CBD) on sleep. One of the most recent studies to look at healthy volunteers and objective measurements, patients were administered treatments using an oromucosal spray during a 30-min period from 10 p.m. Measures included EEG performance, sleep onset latency, and subjective assessments of sleepiness and mood. Results indicated no significant effect on sleep with 15 mg of THC; however, measures of polysomnography indicated decreased latencies to early morning sleep the next day. Administration of both the 5 mg and 15 mg THC/CBD showed a decrease in Stage 3 sleep with the higher dose demonstrating increased wakefulness. As a result, it was concluded that the activating properties of CBD and the sedative properties of THC could function together to induce sleep while counteracting daytime sleepiness. Regarding negative outcomes, two studies identified no significant reported changes or effects on sleep, though treatment periods

were short and sleep measures were non-validated, secondary outcomes (Johnson et al., 2010; Vaney et al., 2004).

2.5 Discussion

One of the main findings of this critical review is that many studies have suggested that the use of THC and THC-derivatives, alone or in combination with CBD, may improve self-reported sleep quality, sleep disturbances, and decrease sleep onset latency. Despite this, the vast majority of these studies investigated sleep as a secondary outcome. Although "sleep" remains one of the main reasons people seek medicinal marijuana, to date there is a surprising lack of placebo-controlled controlled trials examining the use of cannabinoids specifically for treatment of sleep disorders. In addition, many available studies used non-standardized, non-validated questionnaires and the use of validated objective and subjective sleep measures is strongly encouraged in future research. In addition, there remains a large gap in the literature regarding the extent of potential side effects associated with the use of cannabinoids for sleep disorders.

Available pharmacological treatments for insomnia and primary sleep disorders include options such as benzodiazepines and nonbenzodiazepine hypnotics. Many other medications are used off-label for the treatment of these symptoms, such as sedating antidepressants (i.e., trazodone, mirtazapine), and neuroleptics such as quetiapine, chlorpromazine, among others. Unfortunately, many of these medications, while effective, are limited by adverse events, such as daytime sedation, weight gain, metabolic syndrome, and addiction liability (Victorri-Vigneau, Dailly, Veyrac, & Jolliet, 2007).

Similarly, cannabinoids have been also associated with multiple short- and long-term adverse events such as dizziness, cognitive impairment, increased risk of motor vehicle accidents, psychosis, dependence, depression, and anxiety (Budney, Roffman, Stephens, & Walker, 2007; Fischer et al., 2017; Moore et al., 2007; Wang, Collet, Shapiro, & Ware, 2008). In addition to adverse events, some medications used to treat insomnia, including benzodiazepines and sedating antidepressants, can affect sleep architecture (Dujardin, Pijpers, & Pevernagie, 2018). Interestingly, Carley et al. (2018) and Prasad, Radulovacki, and Carley (2013) did not find any objective changes in sleep (%REM, %NREM) when patients with OSA were treated with dronabinol. This suggests that certain cannabinoid preparations (or dosing) may have fewer effects on sleep architecture as compared to traditional medications. However, these findings are not in keeping with data from other studies that demonstrated changes in objective sleep measures following administration of various formulations of cannabis/cannabinoids (Hosko et al., 1973; Nicholson et al., 2004; Pivik et al., 1972; Tassinari et al., 1976). This indicates that the patient population and/or the preparation/dosing of cannabinoids may be an important factor in potential effects on sleep architecture. While the goal of this article was to provide a review on clinical research examining the effects of cannabis/cannabinoids on sleep, other studies examined the effects of recreational cannabis use on sleep. This research was mostly performed in the 1970s–1980s and consisted of small open label studies. A full review of this research is beyond the scope of this current article and has been reviewed elsewhere (Gates, Albertella, & Copeland, 2014). Nevertheless, Gates, Albertella, and Copeland (2014) noted significant concerns in the quality of the studies including small sample

sizes and lack of control for multiple mediating factors. The authors did note that recreational cannabis use tended to impact slow wave sleep and Stage 2 sleep, with an inconsistent trend toward decreasing slow wave sleep and increasing Stage 2 sleep. An inconsistent decrease in sleep onset latency was also noted. No significant trend was noted for total sleep time, sleep quality or REM sleep (Gates et al., 2014). There is also the concern that many of the participants were prior cannabis users and may have become tolerant to the effects of the drug (Jones, Benowitz, & Herning, 1981).

While interpreting the data from these studies, there are several limitations to be aware of. First, the sample sizes of most of the studies discussed are quite small, limiting the statistical power of the results. Second, the majority of the studies examined cannabinoids effect on sleep as a secondary outcome, primarily focusing on cannabinoids in the treatment of another primary illness (i.e., chronic pain, spasticity, etc.). As a result, many of the studies fail to control for the improvement in the primary outcome as a mediating factor resulting in the improvement of sleep related symptoms. Lastly, many of the trials relied on subjective measures of sleep rather than validated methods or objective techniques, such as actigraphy or polysomnography. To address these limitations, future studies will require randomized, placebo-controlled trials designed to investigate sleep as the primary outcome, larger sample sizes, validated subjective measures, and objective assessments. In addition, rather than examining sleep as a secondary measure in the context of other illnesses, future work should examine the effects of cannabinoids in individuals with well-defined sleep disorders. Other methodological issues that required further investigation is the optimal dosing of each specific cannabinoid, as well as the

optimal balance of THC:CBD ratio for treatment of sleep disorders, and potential carry-over effects, since most clinical trials did not perform blood or urine cannabis testing at screening/enrollment.

In conclusion, available evidence suggests that administration of THC and THC-derivatives, alone or in combination with CBD, may improve self-reported sleep. However, randomized, placebo-controlled trials designed to specifically investigate the potential benefits or harms (e.g., side effects) of the use of cannabinoids for sleep disorders are required before any firm conclusion can be made. Given the high prevalence of sleep disorders, the suboptimal treatments currently available, and the dynamic regulatory cannabis landscape, these studies are urgently needed.

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2.7 Declaration of Conflicting Interests

The authors have no conflicts of interest to disclose regarding the content of this article.

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2.9 Figures and Tables

Table 1

Clinical Trials

Author, Year	**Study Design**	**Sample** (Age, Type of Patient)	**Intervention** (Dose, Type of cannabinoids used, Time period)	**Control Group**	**Outcome** (Related to sleep, Subjective/Objective, Validated/Non-validated)	**Results**
Beaulieu (2006)	Randomized, double-blind, placebo-controlled	**Age:** 18-75 **Patient type:** Patients undergoing major surgery	**Type of cannabinoid:** Nabilone **Dose(s):** 1mg or 2mg at 8hr intervals **Time period:** 24hrs	Yes	**Outcome(s):** - Numerical Rating Scale (NRS) on sleep quality **Subjective** **Non-validated**	No significant differences in sleep quality
Bedi et al. (2010)	Within-subjects, double-blind, placebo-controlled	**Age:** 21-50 **Patient type:** HIV-positive marijuana smokers	**Type of cannabinoid:** Dronabinol **Dose(s):** 5mg four times a day for 2 days, then 10mg four times a day for 14 days **Time period:** 16 days	No	**Outcome(s):** - Nightcap sleep monitor (sleep latency, number of awakenings, sleep efficiency) - Visual analogue scales **Objective + Subjective** **Validated**	Days 1-8: Significant increased sleep efficiency; Significant decreased minutes awake; Significant increased self-reported sleep satisfaction; Significant decreased self-reported frequent wakings
Berman, Symonds, & Birch (2004)	Randomized, double-blind, placebo-controlled; crossover	**Age:** 23-63 **Patient type:** Patients with at least one avulsed root and baseline pain score	**Type of cannabinoid:** Sativex (2.7mg THC; 2.5mg CBD) **Dose(s):** Maximum of eight sprays at any one time or within 3hr	Yes (crossover)	**Outcome(s):** - BS-11 scale of sleep quality **Subjective** **Non-validated**	Significant increased self-reported sleep quality; Significant decreased self-reported sleep disturbances

		over 4 on an 11-point scale	period and 48 sprays within any 24hr period **Time period:** Three 2-week treatment periods			
Bestard & Toth (2011)	Open-label, exploratory	**Patient type:** Adult patient with peripheral neuropathy and neuropathic pain	**Type of cannabinoid:** Nabilone **Dose(s):** Flexible daily dose of 1-3 mg/day **Time period:** 6 months	No	**Outcome(s):** - Medical Outcomes Study Sleep Scale (MOSSS) **Subjective** **Validated**	Significant improvement in sleep adequacy and sleep problems index with nabilone monotherapy; Sleep improvements also in adjuvant gabapentin group
Blake, Robson, Ho, Jubb, & McCabe (2006)	Randomized, double-blind, placebo-controlled	**Patient type:** Adult patients with rheumatoid arthritis	**Type of cannabinoid:** Sativex **Dose(s):** Starting at one actuation, increased by one every 2 days to a maximum of 6 actuations **Time period:** 5 Weeks	Yes	**Outcome(s):** - NRS on sleep quality **Subjective** **Non-validated**	Significant improvements in self-reported sleep quality
Brady et al. (2004)	Open-label, exploratory	**Age:** 18-65 **Patient type:** Patients with advanced MS and lower urinary tract symptoms	**Type of cannabinoid:** THC only, then THC:CBD (2.5mg THC; 2.5mg CBD) **Dose(s):** Maximum daily dose of 120mg of THC (48 sprays) **Time period:** 16 Weeks	No	**Outcome(s):** - VAS for sleep **Subjective** **Non-validated**	Significant increased self-reported sleep quality at 8 weeks of only THC; Improvement in sleep disruptions
Brisbois et al. (2011)	Randomized, double-blind, placebo-controlled	**Patient type:** Adult patients with advanced cancer	**Type of cannabinoid:** Dronabinol **Dose(s):** Starting at 2.5mg/day, to 5mg/day; Patients had option to increase to 20mg/day **Time period:** 18 days	Yes	**Outcome(s):** - Side Effect Survey with measure of sleep quality **Subjective** **Non-validated**	Significant improvements in self-reported sleep quality

Cameron et al. (2014)	Retrospective	**Age:** 19-55 **Patient type:** Inmate patients prescribed a single dose or more of nabilone for mental illness	**Type of cannabinoid:** Nabilone **Dose(s):** Mean initial dose: 1.4mg Mean final dose: 4.0mg **Time period:** Range: 1 day-36 weeks	No	**Outcome(s):** - Reported sleep hours and nightmares **Subjective Non-validated**	Significant improvement in PTSD associated nightmares and insomnia
Carley et al. (2018)	Randomized, double-blind, placebo-controlled	**Age:** 21-65 **Patient type:** Patients with moderate or severe obstructive sleep apnea	**Type of cannabinoid:** Dronabinol **Dose(s):** 2.5mg/day or 10mg/day **Time period:** 6 weeks	Yes	**Outcome(s):** - Polysomnography (PSG) (Maintenance of wakefulness) - Epworth Sleepiness Scale (ESS) to measure sleepiness **Objective + Subjective Validated**	Dronabinol 10mg/day: reduced ESS score by -3.8 ± 0.8 from baseline and -2.3 ± 1.2 from placebo; No changes in PSG in any treatment group
Collin et al. (2010)	Randomized, double-blind, placebo-controlled	**Patient type:** Adult patients with MS spasticity	**Type of cannabinoid:** Sativex **Dose(s):** Maximum of eight actuations in 3hrs, and 24 actuations in 24hrs **Time period:** 14 weeks	Yes	**Outcome(s):** - NRS on sleep quality **Subjective Non-validated**	Significant improvements in self-reported sleep quality of patients with >30% improvement in mean spasticity from baseline
Côté et al. (2016)	Randomized, double-blind, placebo-controlled	**Age:** 18-80 **Patient type:** Patients with head and neck carcinomas	**Type of cannabinoid:** Nabilone **Dose(s):** 0.5mg/day, increased to 1mg/day, increased to maximum of 2mg/day **Time period:** 11 weeks	Yes	**Outcome(s):** - Quality of Life Questionnaire (QLQ) (a few questions on sleep) **Subjective Non-validated**	No significant differences in sleep quality
Cousens & DiMascio (1973)	Double-blind, placebo-	**Age:** 21-40 **Patient type:** Male patients	**Type of cannabinoid:** THC **Dose(s):** 10mg, 20mg, 30mg	Yes (crossover)	**Outcome(s):** - Interview on overall sleep (sleep induction, time to fall	Each dose of THC significantly reduced time it took to fall asleep; No effect on sleeping

	controlled; crossover	with sleep difficulties			asleep, sleep interruption) **Subjective** **Non-validated**	pattern; Decrease in sleep interruptions; Increase in time slept
Farabi et al. (2014)	Exploratory	**Age:** 21-64 **Patient type:** Patients with moderate to severe OSA	**Type of cannabinoid:** Dronabinol **Dose(s):** Starting dose of 2.5mg/day to a maximum of 10mg/day if well-tolerated **Time period:** 3 weeks	No	**Outcome(s):** - Polysomnography **Objective** **Validated**	Significant shift in EEG power toward delta and theta frequencies; Significant increase in strengthening ultradian rhythms in sleep leading to decrease in daytime sleepiness; No significant changes in overall sleep efficiency
Frank et al. (2008)	Randomized, double-blind, placebo-controlled; crossover	**Age:** 24-84 **Patient type:** Patients with chronic neuropathic pain	**Type of cannabinoid:** Nabilone **Dose(s):** Maximum of 2mg/day **Time period:** Two 6-week treatment periods	Yes (crossover)	**Outcome(s):** - Sleep diary (average number of hours slept each night) **Subjective** **Non-validated**	No significant differences in sleep quality
Fraser (2009)	Open-label, exploratory	**Patient type:** Adults patients with PTSD and treatment-resistant nightmares	**Type of cannabinoid:** Nabilone **Dose(s):** 0.5mg/day self-titrated to a maximum of 6mg/day **Time period:** Ongoing therapy if effective	No	**Outcome(s):** - Sleep diary (average number of hours slept each night) **Subjective** **Non-validated**	Significant improvements in self-reported sleep quality; Significant reduction of nightmares in 72% of patients
Gorelick et al. (2013)	Open-label, exploratory, escalating-dose	**Age:** 18-45 **Patient type:** Male chronic cannabis smokers	**Type of cannabinoid:** Dronabinol **Dose(s):** Starting dose of 40mg/day to a maximum of 120mg/day **Time period:** 1 week	No	**Outcome(s):** - St. Mary's Hospital Sleep Questionnaire - Pharmacokinetics **Objective + Subjective** **Validated**	Significantly shorter sleep latency; Significant improvement in self-reported difficulty falling asleep; Significant improvement in self-reported daytime sleepiness
Haney et al. (2007)	Placebo-controlled,	**Age:** 21-50 **Patient type:**	**Type of cannabinoid:**	No	**Outcome(s):** - Nightcap sleep	Improvement in total time spent asleep (not

	within subjects	HIV-positive marijuana smokers	THC and dronabinol **Dose(s):** 2% or 3.9% THC 4x/day, then 5mg or 10mg dronabinol 4x/day **Time period:** Two 4-day periods		monitor (sleep latency, number of awakenings, sleep efficiency) - Visual analogue scales **Objective + Subjective** **Validated**	significant); Significant improvement in subjective sleep ratings in high dose THC group
Hosko et al. (1973)	Exploratory, single-blind	**Age:** 24-28 **Patient type:** Healthy male volunteers	**Type of cannabinoid:** THC **Dose(s):** Starting dose of 200mg/kg to a maximum of 400mg/kg **Time period:** 7 nights	No	**Outcome(s):** - Polysomnography **Objective** **Validated**	No consistent pattern of sleep alteration in group as a whole; Changes in sleep architecture by case
Jetly et al. (2015)	Randomized, double-blind, placebo-controlled; crossover	**Age:** 18-65 **Patient type:** Male military personnel with PTSD	**Type of cannabinoid:** Nabilone **Dose(s):** Starting dose of 0.5mg to a maximum of 3.0mg **Time period:** 7- week treatment period	Yes (crossover)	**Outcome(s):** - CAPS recurrent distressing dreams item and difficulty falling or staying asleep item - Sleep diary (Total sleep time and number of awakenings) **Subjective** **Non-validated**	Significant self-reported improvement in distressing dream score; No significant differences on sleep quality and quantity in CAPS items or sleep diary
Johnson et al. (2010)	Randomized, double-blind, placebo-controlled	**Patient type:** Adult patients with cancer-related pain	**Type of cannabinoid:** Sativex **Dose(s):** Maximum of eight sprays at any one time or within 3hr period and 48 sprays within any 24hr period **Time period:** 2 weeks	Yes	**Outcome(s):** - NRS on sleep quality **Subjective** **Non-validated**	No significant differences in sleep quality
Langford et al. (2013)	**Phase A:** Randomized,	**Patient type:** Adult patients	**Type of cannabinoid:** Sativex	Yes	**Outcome(s):** - NRS on sleep	Phase A: No significant differences in sleep

	double-blind, placebo-controlled **Phase B:** Open-Label	with MS and chronic neuropathic pain resistant to other treatments	**Dose(s):** Maximum of 12 sprays/day **Time period:** Phase A: 98 days Phase B: 28 days		quality **Subjective** **Non-validated**	quality Phase B: Improvement in sleep quality noted in randomized withdrawal phase
Narang et al. (2008)	Randomized, double-blind, placebo-controlled; crossover	**Patient type:** Adults with chronic noncancerous pain taking opioids	**Type of cannabinoid:** Dronabinol **Dose(s):** 10mg or 30mg over course of three 8-hour visits **Time period:** Three 8-hour visits	Yes (crossover)	**Outcome(s):** - Medical Outcomes Study Sleep Scale (MOSSS) - Brief Pain Inventory (sleep interference item) **Subjective** **Validated**	Significant improvements in self-reported sleep disturbances; Significant improvements in sleep adequacy; Significant improvements in pain interfering with sleep
Nicholson, Turner, Stone, & Robson (2004)	Double-blind, placebo-controlled; crossover	**Age:** 21-34 **Patient type:** Healthy volunteers	**Type of cannabinoid:** 15mg THC 5mg THC:5mg CBD 15mg THC:15mg CBD **Dose(s):** 6 actuations of 100 ml during 30-minute period given at 6-minute intervals **Time period:** 4 treatment nights	Yes (crossover)	**Outcome(s):** - Polysomnography (PSG) - Stanford Sleepiness Scale - Sleep latency test **Objective + Subjective** **Validated**	No significant differences in subjective sleepiness, sleep onset, or duration; No significant difference of 15mg THC on sleep architecture but decreased sleep latency noted; Significant decrease in stage 3 sleep and increase in wakefulness with higher dose combination of concomitant administration
Novotna et al. (2011)	Randomized, double-blind, placebo-controlled; enriched	**Patient type:** Adult patients with MS	**Type of cannabinoid:** Sativex **Dose(s):** Maximum of 12 sprays/day **Time period:** 16 treatment weeks (total)	Yes	**Outcome(s):** - NRS on sleep disruption **Subjective** **Non-validated**	Significant improvements in self-reported sleep disruptions

Nurmikko et al. (2007)	Randomized, double-blind, placebo-controlled	**Patient type:** Adult patients with neuropathic pain and allodynia	**Type of cannabinoid:** Sativex **Dose(s):** Maximum of eight sprays within 3hr period and 48 sprays within any 24hr period **Time period:** 5 weeks	Yes	**Outcome(s):** - Verbal rating scale for sleep disturbance **Subjective Non-validated**	Significant improvements in sleep disturbances maintained until end of study
Pivik et al. (1972)	Exploratory	**Patient type:** Healthy adult male volunteers	**Type of cannabinoid:** THC or Synhexl **Dose(s):** 61-259 mg/kg THC or 733-777 mg/kg Synhexl **Time period:** 1 day	No	**Outcome(s):** - Polysomnography **Objective Validated**	Increase in stage IV sleep and decrease in REM sleep; reduction in stage I sleep; reduction in time awake after sleep onset at highest dose level
Portenoy et al. (2012)	Randomized, double-blind, placebo-controlled	**Patient type:** Adult patients with advanced cancer and chronic pain	**Type of cannabinoid:** Sativex **Dose(s):** Low: 1-4 sprays/day Medium: 6-10 sprays/day High: 11-16 sprays/day **Time period:** 5 weeks	Yes	**Outcome(s):** - NRS on sleep disruption **Subjective Non-validated**	Significant improvements in self-reported sleep disruptions in low dose group (p=0.003) and slight improvements in medium (p=0.260) and high dose groups (p=0.784)
Prasad et al. (2013)	Proof-of-concept, dose escalation	**Age:** 21-65 **Patient type:** Adult patients with baseline Apnea Hypopnea Index (AHI) >15/h	**Type of cannabinoid:** Dronabinol **Dose(s):** 2.5, 5.0, or 10.0mg/day **Time period:** 21 days	No	**Outcome(s):** - Polysomnography - Stanford Sleepiness Scale (SSS) **Objective + Subjective Validated**	Significant improvement in AHI from baseline to night 21; no degradation of sleep architecture; Significant improvement in SSS
Rog, Nurmikko, Friede, & Young (2005)	Randomized, double-blind, placebo-controlled	**Patient type:** Adult patients with MS and central	**Type of cannabinoid:** Sativex **Dose(s):** Maximum of eight sprays within 3hr period and 48	Yes	**Outcome(s):** - NRS on sleep disturbance **Subjective Non-validated**	Significant improvements in self-reported sleep disturbances (p=0.003)

		neuropathic pain	sprays within any 24hr period **Time period:** 4 weeks			
Roitman et al. (2014)	Open-label, exploratory	**Patient type:** Adult patients with chronic PTSD	**Type of cannabinoid:** THC **Dose(s):** 5mg twice a day **Time period:** 3 weeks	No	**Outcome(s):** - Pittsburgh Sleep Quality Index (PSQI) to measure sleep quality and sleep disturbances - Nightmare Frequency Questionnaire (NFQ) - Nightmare Effects Survey (NES) **Subjective** **Validated**	Significant improvements in sleep quality and frequency of nightmares
Serpell et al. (2014)	Randomized, double-blind, placebo-controlled	**Patient type:** Adult patients with peripheral neuropathic pain	**Type of cannabinoid:** Sativex **Dose(s):** Maximum of eight sprays at any one time or within 3hr period and 24 sprays within any 24hr period **Time period:** 14-week treatment period	Yes	**Outcome(s):** - NRS on sleep quality **Subjective** **Non-validated**	Significant improvements in self-reported sleep quality (p=0.0072)
Tassinari et al. (1976)	Exploratory	**Age:** 21-25 **Patient type:** Healthy volunteers	**Type of cannabinoid:** THC **Dose(s):** Single dose of 0.7-1mg/kg, 1-1.4mg/kg, or 0.8-0.9mg/kg **Time period:** 1 day	No	**Outcome(s):** - Polysomnography **Objective** **Validated**	Suppression of REM sleep; Increase of stage II sleep; Decrease of stage III and IV sleep.
Toth et al. (2012)	Randomized, double-blind, placebo-controlled; enriched	**Age:** 18-80 **Patient type:** Patients with diabetic peripheral neuropathic	**Type of cannabinoid:** Nabilone **Dose(s):** Flexible dose 1-4mg/day **Time period:** 9-week treatment period	Yes	**Outcome(s):** - Medical Outcomes Study Sleep Scale (MOSSS) **Subjective** **Validated**	Significant improvements in sleep disruption scores at weeks 6, 8, 9

		pain with pain score > 4				
Vaney et al. (2004)	Randomized, double-blind, placebo-controlled; crossover	**Patient type:** Adult patients with MS	**Type of cannabinoid:** 2.5mg THC; 0.9mg CBD **Dose(s):** Starting dose of 15mg THC/day to maximum of 30mg THC/day **Time period:** 14-day treatment period	Yes (crossover)	**Outcome(s):** - Sleep diary (sleep disturbances) **Subjective Non-validated**	No significant differences in sleep
Wade, Robson, House, Makela & Aram (2003)	Randomized, double-blind, placebo-controlled; crossover	**Patient type:** Adult patients with a neurological diagnosis	**Type of cannabinoid:** THC only (2.5mg), CBD only (2.5mg), THC:CBD (1:1) preparation **Dose(s):** Maximum of 120mg/day **Time period:** Four 2-week treatment periods	Yes (crossover)	**Outcome(s):** - Visual Analogue Scale (VAS) to measure sleep quality **Subjective Non-validated**	Significant improvements in self-reported sleep quality with THC:CBD treatment
Wade, Makela, Robson, House & Bateman (2004)	Randomized, double-blind, placebo-controlled	**Patient type:** Adult patients with MS	**Type of cannabinoid:** Sativex **Dose(s):** Maximum of 120mg THC and 120mg of CBD per day with no more than 20mg in a 3hr period **Time period:** 6 weeks	Yes	**Outcome(s):** - Visual Analogue Scale (VAS) to measure sleep quality **Subjective Non-validated**	Significant improvements in self-reported quality of sleep (p=0.047)
Ware et al. (2010a)	Randomized, double-blind, placebo-controlled; crossover	**Patient type:** Adult patients with fibromyalgia and comorbid chronic insomnia	**Type of cannabinoid:** Nabilone **Dose(s):** 0.5-1mg **Time period:** Two 2-week treatment periods	Yes (crossover)	**Outcome(s):** - Leeds Sleep Evaluation Questionnaire (LSEQ) to measure sleep quality - Insomnia Severity Index (ISI) to measure insomnia severity	Greater improvement in sleep quality compared to amitriptyline (ISI difference of 3.2; LSEQ difference of 0.5)

					Subjective **Validated**	
Ware et al. (2010b)	Randomized, double-blind, placebo-controlled; crossover	**Patient type:** Adult patients with post-traumatic or postsurgical neuropathic pain	**Type of cannabinoid:** THC (potencies of 2.5%, 6.0%, 9.4%) **Dose(s):** 25mg/3x day **Time period:** Four 14-day treatment periods	Yes (crossover)	**Outcome(s):** - LSEQ to measure sleep quality **Subjective** **Validated**	Significant improvements in self-reported sleep quality with 9.4% THC
Weber et al. (2010)	Randomized, double-blind, placebo-controlled; crossover	**Patient type:** Adult patients with ALS and moderate to severe cramping	**Type of cannabinoid:** Dronabinol **Dose(s):** 5mg/2x day **Time period:** Two 2-week treatment periods	Yes (crossover)	**Outcome(s):** - Sleep Disorder Questionnaire (SDQ) items measuring sleep quality **Subjective** **Validated**	No significant differences in sleep quality
Zajicek et al. (2003)	Randomized, double-blind, placebo-controlled	**Age:** 18-64 **Patient type:** Patients with MS	**Type of cannabinoid:** Cannador (2.5mg THC; 1.25mg CBD) or Dronabinol **Dose(s):** Based on body weight with a maximum of 25mg/day **Time period:** 14-week treatment period	Yes	**Outcome(s):** - Category rating scale (self-report on sleep quality) **Subjective** **Non-validated**	Significant improvements in self-reported sleep quality
Zajicek, Hobart, Slade, Barnes, & Mattison (2012)	Randomized, double-blind, placebo-controlled	**Age:** 18-64 **Patient type:** Patients with MS	**Type of cannabinoid:** Cannador (2.5mg THC; 0.8-1.8mg CBD) **Dose(s):** Starting dose of 5mg/day to a maximum of 25mg/day **Time period:** 12 weeks	Yes	**Outcome(s):** - NRS on sleep disturbances **Subjective** **Non-validated**	Significant improvements in self-reported sleep disturbances

Table 2

Risk of Bias Assessment of RCTs

Study	**Random Sequence Generation** (selection bias)	**Allocation Concealment** (selection bias)	**Blinding of Participants and Personnel** (performance bias)	**Blinding of Outcome Assessment** (detection bias)	**Incomplete Outcome Data** (attrition bias)	**Selective Reporting** (reporting bias)	**Other**	**Notes**
Beaulieu (2006)	+	?	+	+	+	+	+	Does not mention how the randomization was performed
Berman et al. (2004)	+	+	+	+	+	+	?	Possible carry-over effect
Blake et al. (2006)	+	?	?	?	+	+	+	Does not state how participants were block randomized; does not say how they were allocated; does not mention whether the presentation of medications was similar; Did not mention blinding assessment
Carley et al. (2018)	+	+	+	+	+	+	?	Groups sizes were not fully balanced
Collin et al. (2010)	?	?	+	?	+	?	+	Does not state how participants were block randomized; does not say how they were allocated; Does not mention blinding of assessment; Reporting

							of nonsignificant results were overemphasized toward the active treatment
Jetly et al. (2015)	?	+	+	+	+	+	+	Does not mention how participants were randomized
Johnson et al. (2010)	?	?	+	+	?	+	+	Does not state how participants were block randomized; does not say how they were allocated; Does not mention how missing data was dealt with
Langford et al. (2013)	+	+	+	+	+	+	+	
Narang et al. (2008)	+	+	+	+	+	+	?	Possible carry-over effect
Nicholson et al. (2004)	?	?	+	+	+	+	+	Does not state how participants were block randomized; does not say how they were allocated
Novotna et al. (2011)	?	?	?	?	+	+	?	Does not state how participants were block randomized; does not say how they were allocated; Not enough information regarding blinding; Enriched study design
Nurmikko et al. (2007)	+	+	+	+	?	+	+	Does not mention how missing data was dealt with

Portenoy et al. (2012)	+	+	+	+	+	+	+	
Rog et al. (2005)	+	+	+	+	+	+	+	
Serpell et al. (2014)	+	+	+	+	?	+	+	Larger dropout rate in the active treatment group
Toth et al. (2012)	+	+	−	+	+	+	?	Significant unmasking; Enriched study design; Possible carry-over effect
Vaney et al. (2004)	+	+	+	+	+	+	+	
Wade et al. (2003)	+	+	?	+	+	+	+	Open label rescue active medication may affect unmasking
Wade et al. (2004)	+	+	+	+	+	+	+	
Ware et al. (2010a)	+	+	+	+	+	+	+	
Ware et al. (2010b)	+	?	+	+	+	+	+	Not enough information on randomization allocation
Weber et al. (2010)	+	+	+	+	+	+	+	
Zajicek et al. (2003)	+	+	−	+	+	+	+	Significant unmasking in the active treatment group
Zajicek et al. (2012)	+	+	+	+	?	+	+	Larger dropout rate in the active treatment group

Note. Low risk = +; Unclear risk = ?; High risk = −.

Chapter 3: The Use of Cannabinoids for Insomnia in Daily Life: Naturalistic Study

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Abstract

Background: Insomnia is a prevalent condition that presents itself at both the symptom and diagnostic levels. Although insomnia is one of the main reasons individuals seek medicinal cannabis, little is known about the profile of cannabinoid use or the perceived benefit of the use of cannabinoids in daily life.

Objective: We conducted a retrospective study of medicinal cannabis users to investigate the use profile and perceived efficacy of cannabinoids for the management of insomnia.

Methods: Data were collected using the Strainprint app, which allows medicinal cannabis users to log conditions and symptoms, track cannabis use, and monitor symptom severity pre- and post-cannabis use. Our analyses examined 991 medicinal cannabis users with insomnia across 24,189 tracked cannabis use sessions. Sessions were analyzed, and both descriptive statistics and linear mixed-effects modeling were completed to examine use patterns and perceived efficacy.

Results: Overall, cannabinoids were perceived to be efficacious across all genders and ages, and no significant differences were found among product forms, ingestion methods, or gender groups. Although all strain categories were perceived as efficacious, predominant indica strains were found to reduce insomnia symptomology more than cannabidiol (CBD) strains (estimated mean difference 0.59, SE 0.11; 95% CI 0.36-0.81; adjusted P<.001) and predominant sativa strains (estimated mean difference 0.74, SE

0.16; 95% CI 0.43-1.06; adjusted P<.001). Indica hybrid strains also presented a greater reduction in insomnia symptomology than CBD strains (mean difference 0.52, SE 0.12; 95% CI 0.29-0.74; adjusted P<.001) and predominant sativa strains (mean difference 0.67, SE 0.16; 95% CI 0.34-1.00; adjusted P=.002).

Conclusions: Medicinal cannabis users perceive a significant improvement in insomnia with cannabinoid use, and this study suggests a possible advantage with the use of predominant indica strains compared with predominant sativa strains and exclusively CBD in this population. This study emphasizes the need for randomized placebo-controlled trials assessing the efficacy and safety profile of cannabinoids for the treatment of insomnia.

Keywords

medicinal cannabis, insomnia, symptom management, linear mixed-effects

3.1 Introduction

3.1.1 Background

With the growing interest in the therapeutic and medicinal uses of cannabis, there is an increased need to better understand the harms and benefits of acute and long-term therapeutic use of cannabinoids. Among individuals who use medicinal cannabis in Canada, 42% report using cannabis 2-3 times a day, with 40% of users reporting their consumption to be >14 grams per week (Ko et al., 2016). In fact, rates of medicinal cannabis authorization in Canada rose from 8000 in 2014 to 340,000 in 2018 (Turna et al., 2020). Similarly, with nationwide cannabis legalization in October 2018, general cannabis use rates in Canada increased from 14% to 18% between 2018 and 2019 (Rotermann, 2019).

Despite the paucity of randomized placebo-controlled trials, both recreational and medicinal cannabis users report perceptions of a broad spectrum of benefits from cannabis. Among these benefits of the use of cannabis is aiding sleep (Walsh et al., 2013). In fact, in addition to pain and anxiety, insomnia has commonly been reported to be among the top reasons individuals seek medicinal cannabis (Turna et al., 2020). This association is very relevant considering the high rates of insomnia in the general population. It is estimated that approximately 10% of adults experience chronic insomnia (Ferrie et al., 2011), and nearly one-third of all adults suffer from occasional or intermittent insomnia symptoms annually (Ferrie et al., 2011). Longitudinal studies have found that nearly 70% of individuals reporting insomnia symptoms at baseline continue to report symptoms a year later (Morin & Benca, 2012), and 50% continue to report having

symptoms 3 years later. Insomnia is also one of the most common complaints in primary care, often presenting itself at both symptom and diagnostic levels (Morin & Benca, 2012). Characterized by difficulty in falling asleep, staying asleep, or having a nonrestorative sleep, insomnia negatively affects functioning, quality of life, and mental health (Levenson et al., 2015). In addition, insomnia often co-occurs with common medical and psychiatric conditions (Morin & Benca, 2012). Individuals experiencing these comorbidities report greater impairments in psychosocial and cognitive functioning compared with individuals without sleep disturbances (Ohayon, 2002; Buysse et al., 2008; Morin & Benca, 2012; Levenson et al., 2015; Chen et al., 2017).

3.1.2 Cannabinoids for Insomnia

Recent reviews have concluded that the current evidence of the benefits of using cannabinoids for insomnia symptoms are largely driven by clinical trials that used cannabinoids for the treatment of other conditions, such as pain or multiple sclerosis (Gates et al., 2014; Babson et al., 2017; Kuhathasan et al., 2019). Similarly, although some previous studies have examined recreational and medicinal cannabis use in naturalistic samples, very few have focused on insomnia as a primary outcome (Pearce et al., 2014; Stith et al., 2018). In one study, 95 medicinal cannabis users were surveyed on the effects of cannabis products used for various conditions and symptoms (Pearce et al., 2014). The results indicated a statistically significant preference toward *Cannabis indica* products to help with sedation and sleep (Pearce et al., 2014). In addition, the same study reported that users also preferred these products for insomnia, encouraging further

research focusing on the condition (Pearce et al., 2014). In another study, a mobile app collecting data on medicinal cannabis in naturalistic conditions was used to measure the self-reported effectiveness and side effects of cannabis (Stith et al., 2018). The study examined 2332 users across 10,535 tracked cannabis sessions (Stith et al., 2018). The results indicated significant reductions in symptom severity across all reported symptoms, with significantly more relief in anxiety- and depression-related symptoms than pain symptoms (Stith et al., 2018). Notably, in this particular study, insomnia was examined as a symptom of anxiety and presented the largest symptom relief score across all examined symptoms following cannabis consumption (Stith et al., 2018).

Most relevantly, a recent naturalistic study that examined cannabis use for insomnia in a sample of 409 participants across 1056 sessions reported significant reductions in symptom severity; however, these findings were limited to raw, natural medical cannabis flowers and lacked information on the perceived efficacy of various cannabis product forms. Furthermore, this study was limited by a lack of information on patient demographics, as the information collected from users did not include key demographic data, such as age and gender (Vigil et al., 2018). Since the legalization of cannabis in Canada in 2018, research regulations for the drug remain quite stringent (Ko et al., 2016). Similarly, because of its status as a schedule 1 drug in the United States, it is under investigated for therapeutic purposes (Shen, 2014; Rhodes et al., 2016; Stith & Vigil, 2016; Mead, 2019). Therefore, not only is there a major gap in studies assessing insomnia as the primary outcome, but also a lack of scientific literature on the use of cannabis products that are currently being consumed by the general public (Gates et al.,

2014; Babson et al., 2017; Kuhathasan et al., 2019). To help address these gaps, we conducted a retrospective study to investigate the perceived effectiveness of the use of cannabinoids in treating insomnia symptoms in a large, naturalistic sample of Canadians. We also describe the key demographic characteristics of these individuals, such as age and gender distribution, types of cannabinoid use, and methods of ingestion.

3.2 Methods

3.2.1 Overview of Strainprint App

We conducted a retrospective study examining cannabis use for the management of insomnia symptoms using anonymous archival data obtained from the medicinal cannabis–tracking app Strainprint (Strainprint Technologies Ltd). Strainprint is a Canadian app with a large database of medical and recreational cannabis users with >90 million data points and 2 million reported patient outcomes. The app allows users to track and monitor changes in their symptoms as a function of different doses, strains, and forms of cannabis. It engages users through a loyalty rewards system where users earn points for tracking sessions of cannabis use. Through Strainprint, users are able to record medical conditions, symptoms being treated, methods of ingestion, doses, emotive effects, pre- and post-medication ratings, and cannabis product constituents by batch for each tracked session. Tracked information can also be shared with health care providers. On initial use of the app, individuals are prompted to enter basic demographic information, such as year and month of birth, gender, and the conditions and symptoms that they wish to treat. When individuals are ready to track their medication session, they open the app before

using cannabis and select the relevant symptoms they wish to treat from a dropdown list of their previously chosen symptoms. Users are then taken through a set of steps where they are first prompted to rate the severity of their symptoms on a 11-point numeric rating scale (0=least severe and 10=very severe) before medication. Next, individuals select the cannabis they are using by product name and batch. Strainprint prepopulates the app with lab-verified cannabis constituents by batch for all medical cannabis products sold by licensed producers in Canada. Data on cannabis content are pulled directly from cannabis distributors. Users then select the product form (flower, oil, capsule, edible, vape pen, or concentrate), route of administration (vape, oil, smoke, edible, pill, tincture, spray, concentrate, dab bubble, dab portable, oral, topical, or transdermal), and dose (drops, mg, ml, or puffs) for that specific session. After an onset period defined by the chosen route of administration (e.g., 20 minutes for smoke and 60 minutes for pill or edible), users are prompted with a push notification (8 hours later for sleep) to complete their session by rating their symptom severity post medication on the same 11-point numeric scale.

Strainprint also provides individuals with a complete history of their use, along with product recommendations based on other users' experiences with the same symptoms. As part of Strainprint's terms of service, individuals agree to share their anonymous information for research and other purposes. In this study, we examined the data of individuals who used medicinal cannabis to manage the severity of insomnia symptoms for the condition of insomnia. Specific variables for this study were determined before data extraction, and the information was subsequently provided by Strainprint stripped of identifiers.

3.2.2 Study Sample

Our study included all tracked sessions between February 27, 2017, and February 28, 2020. The final sample consisted of 991 Canadian medicinal cannabis users with insomnia who used the app to monitor changes in insomnia symptoms across 24,189 recorded sessions. The sample comprised 42.6% (422/991) self-identified male participants and 56.1% (556/991) self-identified female participants (13/991, 1.3% of users did not report gender), ranging in age from 18 to 74 years (mean 36.32, SD 11.65). Additional descriptive statistics on the sample are presented in Figure S1 of supplementary material.

3.2.3 Statistical Analysis

First, we completed a descriptive analysis of the data set by generating information on the specific cannabis use profile for the management of insomnia symptoms. In particular, we examined the frequencies of categorical cannabis use variables such as use time of day, strain categories, product forms, and ingestion methods. These data were further stratified to investigate cannabis use trends by both age and gender. For inferential analyses, our primary analysis focused on the perceived efficacy of cannabis for the management of insomnia symptoms. Efficacy was calculated as the change in insomnia symptomology between pre- and post-medication rates, as reported by users.

Generally, this type of statistical modeling would be completed as a standard regression analysis; however, a standard regression analysis assumes that observations are

independent. In this particular data set, users reported multiple observations, and a standard regression analysis would not account for between-person variability in tracked sessions across users. Therefore, we used linear mixed-effects modeling, a type of regression model that estimates random effects (accounting for between-subject variability) in addition to standard fixed effects (accounting for within-subject variability) regardless of differences in the number of reported observations per user. In essence, this mixed-modeling method estimates random intercepts and slopes, which are then used to make more accurate inferences at the fixed-effects level without violating the independence assumption.

Assumptions for each model were checked to ensure the validity of the models used. Residual plots were examined and were determined to not deviate from the assumptions of linearity, normality, and homoscedasticity. The assumption of independence was met by accounting for tracked session nesting within participants using mixed-effects models. For this analysis, linear mixed-effects modeling was used to predict changes in the perceived efficacy of cannabis use with regard to demographic information (i.e., age and gender) and cannabis use information (i.e., use time of day, product form, and strain category) across tracked sessions. In addition, although several studies have challenged the labeling of strain categories in commercial products, in this naturalistic study, we analyzed this variable as a commercialized label influencing purchasing choices. In all analyses, *P* values were corrected for multiple comparisons using the stringent Bonferroni correction ($P<.05$, Bonferroni corrected).

3.2.4 Ethical Approval

Ethical approval for this research was granted by the Hamilton Integrated Research Ethics Board (project #7162). The study was designed to be compliant with the Health Information Protection Act, 2016.

3.3 Results

3.3.1 Strain Categories for Insomnia

Descriptive statistics examining the percentage of each strain category (i.e., predominant sativa, sativa hybrid, predominant indica, indica hybrid, balanced hybrid, or cannabidiol [CBD]) used for the management of insomnia symptoms across 24,189 tracked sessions are presented in Table 1. Overall, predominant indica and indica hybrid strains were the most commonly used strains for insomnia, whereas predominant sativa and sativa hybrid strains were used least for the management of insomnia symptoms. Notably, although CBD is not traditionally considered a strain category, Strainprint recognizes the variations in tetrahydrocannabinol (THC) or CBD content across different strains and presents a CBD-predominant product category as a strain on the app. Further descriptive statistics of strain categories stratified by age and gender are presented in Figures S2 and S3 in supplementary material.

3.3.2 Cannabis Product Forms and Ingestion Methods for Insomnia

Descriptive statistics examining the frequencies of cannabis product forms (i.e., flower, oil, capsule, edible, vape pen, or concentrate) used for the management of

insomnia symptoms across 24,189 tracked sessions are presented in Table 2. Because of the relatively small number of data points, products in the form of vape pens and concentrates were combined to form an *other* group. Across all age groups and genders, cannabis was most often used in the form of flowers, followed by oil products, for the management of insomnia symptoms. Table 3 presents descriptive statistics examining the frequencies of cannabis ingestion methods (i.e., vape, oil, smoke, edible, pill, tincture, spray, concentrate dab bubbler, dab portable, oral, topical, or transdermal) across all tracked sessions. Again, because of the relatively small number of data points, the categories of concentrate, dab bubbler, dab portable, oral, topical, and transdermal were combined to form a single category. Vaping was the most popular ingestion method across all age groups and genders. All reported results were stratified by age and gender.

3.3.3 Symptom Severity Ratings

Mean symptom severity ratings were examined before and after cannabis use across tracked sessions (N=991 users across 24,819 sessions; Figure 1). Before cannabis use, the mean symptom severity rating across sessions was 7.35 (SD 1.88), whereas the mean symptom severity rating after use was 3.20 (SD 2.37).

3.3.4 Linear Mixed-Effects Model Predictions of Perceived Efficacy

We first examined the perceived efficacy of cannabinoid use for insomnia as a function of gender and found it to be significant across both genders (Table 4). The perceived efficacy of cannabinoid use for insomnia was also significant across all age

groups (Table 5). Comparisons between gender and age can be found in supplementary material (Tables S1 and S2).

Next, we examined whether the time of cannabis use predicted perceived efficacy and found that efficacy was significant regardless of the time of day (Table 6). Because of the nature of the data, information on shift work was not available; therefore, we did not compare efficacy across different use times during the day. More detailed frequency and percentage information of sessions for each use time of the day can be found in Table S3 of supplementary material.

We also examined perceived efficacy as a function of cannabis product forms and found that all product forms were perceived as efficacious (Table 7). Notably, for some product forms (i.e., vape pen and concentrate), there were too few observations to warrant inclusion in primary analyses, even when combined to form a single category. Therefore, of all available product forms, only those making up at least 0.005% of the data set were included in the analyses. There were no significant differences in efficacy among product forms (all P>.05; Table S4, supplementary material).

Finally, we examined perceived efficacy as a function of strain category and found that cannabis was efficacious regardless of the specific strain being used (Table 8). Interestingly, predominant indica strains were found to be more efficacious than CBD (estimated mean difference 0.59, SE 0.11; 95% CI 0.36-0.81; adjusted *P*<.001) and predominant sativa strains (estimated mean difference 0.74, SE 0.16; 95% CI 0.43-1.06; adjusted *P*<.001). Indica hybrid strains were also found to be more efficacious than CBD (estimated mean difference 0.52, SE 0.12; 95% CI 0.29-0.74; adjusted *P*<.001) and

predominant sativa strains (estimated mean difference 0.67, SE 0.16; 95% CI 0.34-1.00; adjusted *P*=.002). Balanced hybrid strains were also found to be more efficacious than CBD (estimated mean difference 0.39, SE 0.13; 95% CI 0.14-0.64; adjusted *P*=.03) and sativa strains (estimated mean difference 0.54, SE 0.17; 95% CI 0.20-0.88; adjusted *P*=.03; Table 9).

3.4 Discussion

3.4.1 Principal Findings

Results from this large naturalistic sample of medicinal cannabis users who tracked their insomnia symptoms before and after cannabis use suggest significant improvements in insomnia symptoms, with no gender differences in perceived efficacy. Notably, this study uses a naturalistic design by analyzing crowdsourced data from a medicinal cannabis–tracking mobile app. With increasing advances in technology, this study presents a unique perspective on a health management self-monitoring tool that examines data on a population scale.

Analyses of product forms and ingestion methods found that cannabis was most often used in the form of flowers or oils and most often ingested via vapes, oils, or smoking. In addition, although all strains were reported to be beneficial for the management of insomnia, predominant indica and indica hybrid strains were found to be more efficacious than CBD and predominant sativa strains. This finding is in contrast with those of a previous study reporting that strains with significantly higher concentrations of CBD were generally preferred by individuals using cannabis to treat

symptoms of insomnia (Belendiuk et al., 2015). Despite this, our findings are in line with results from previous studies that have reported indica and hybrid strains to be among the most frequently used strains for insomnia (Vigil et al., 2018). This same study reported that the most used strains were fairly high in THC content and were combined with high to moderate CBD content.

Another study investigating multiple doses of cannabinoids for sleep reported that administration of both 5 mg/5 mg and 15 mg/15 mg of THC/CBD demonstrated a decrease in stage 3 sleep when compared with placebo, with the higher dose also showing increased states of wakefulness (Nicholson et al., 2004). THC administration on its own demonstrated no significant changes to sleep architecture from placebo; however, the same study found that high doses of THC alone or in combination with CBD resulted in increased subjective sleepiness (Nicholson et al., 2004). From this, the researchers concluded that CBD may have dose-dependent effects on alertness and that the activating and sedating properties of CBD and THC, respectively, could work together to induce sleep and counteract daytime sleepiness (Nicholson et al., 2004). Although few clinical trials have objectively analyzed cannabinoids for sleep with sleep outcomes as primary measures, some preliminary trials have shown that administration of THC and THC-derivatives, alone or in combination with CBD, were associated with subjective improvement in sleep outcomes (Gates et al., 2014; Babson et al., 2017; Kuhathasan et al., 2019). In addition, previous studies examining strain preferences have also reported increased preferences toward indica strains for sleep (Pearce et al., 2014; Piper, 2018; Sholler et al., 2022). In one study, indica was preferred for sedation and sleep, whereas

sativa was preferred to increase energy (Pearce et al., 2014). Another study investigating qualitative responses reported that patients using medicinal cannabis preferred using indica at night to improve sleep (Piper, 2018). In essence, to better understand the efficacy of cannabinoids for insomnia, randomized placebo-controlled studies are needed.

The human endocannabinoid (eCB) system has been increasingly implicated in body and brain homeostasis, including sleep. For instance, the eCB system is thought to play an active role in regulatory processes, such as pain perception, memory, and sleep modulation (Pacher et al., 2006; Stasiłowicz et al., 2021). Although the neurobiological basis of cannabis for sleep is still being understood, overlaps between the neuronal circuitry of sleep and wake states and the eCB system suggest that cannabinoids can contribute to sleep-related mechanisms and physiology (Murillo-Rodríguez, 2008; Murillo-Rodriguez et al., 2011; Kesner & Lovinger, 2020). Therefore, the eCB system has become a growing target in sleep research (Pacher et al., 2006; Murillo-Rodríguez, 2008; Murillo-Rodriguez et al., 2011; Di Marzo, 2018; Kesner & Lovinger, 2020; Stasiłowicz et al., 2021). Despite the perceived benefits of cannabinoids, there remains a lack of placebo-controlled trials that have examined the effects of the drug using validated sleep measures or objective sleep outcomes (Gates et al., 2014; Babson et al., 2017; Kuhathasan et al., 2019). In addition, the current literature on the existence of potential risks, harms, and side effects associated with cannabinoid treatments remain extremely sparse for sleep disorders; however, there is growing evidence that suggests an increased risk of both acute and chronic cognitive impairments (Crean et al., 2011; MacKillop, 2019). Although these risks are poorly understood, research suggests that the

prevalence of these effects is increasing (MacKillop, 2019). Future clinical trials should focus on the benefits and potential harms through the use of validated objective and subjective measures. Because of the highly comorbid nature of insomnia and other sleep disorders, additional variables such as medication interactions, potential side effects, and comorbid diagnoses are also worth investigating.

3.4.2 Limitations

Some limitations should be considered when interpreting the results of this study. First, individual conditions and symptoms were subjectively reported by users on the Strainprint app. Therefore, it is unknown whether subjects will meet the full criteria for insomnia or any other sleep-related disorder. Moreover, individual user data are restricted to the information collected by Strainprint; therefore, additional information that may affect cannabinoid efficacy (e.g., medical history, body size, other concurrent medications, or tolerance) could not be assessed. Another limitation of this study is the lack of a placebo control group. Because data were collected from a sample of medicinal cannabis users, it is possible that individual expectations of cannabinoid efficacy may have attributed to positive post medication ratings. In other words, the large magnitude effect-size observed reflects pharmacological effects and response expectancy (placebo) effects, and the proportionate contribution of each, fundamentally, cannot be ascertained. It is also possible that this study examined the data of individuals who were more likely to find cannabis to be effective, as the Strainprint app is geared toward individuals who wish to improve therapeutic outcomes by tracking their cannabis use. As a result, the sample

may disproportionately represent users who benefit from using cannabis. In addition, the Strainprint app primarily collects data on cannabis use and has very limited data on its potential side effects. Therefore, beyond perceived efficacy, it was not possible to ascertain from the available data whether users experienced any negative side effects from cannabis use.

This study also examined various strain categories; however, distinctions between these strains remain the subject of much debate (Sawler et al., 2015; Piomelli & Russo, 2016; Schwabe & McGlaughlin, 2019). Cannabis has historically been classified into two separate species (*C.sativa* and *C. indica*) with distinct biological effects. However, years of breeding and hybridization have rendered potential distinctions often meaningless (Piomelli & Russo, 2016; McPartland, 2018; Schwabe & McGlaughlin, 2019; de la Fuente et al., 2020). As recreational cannabis use has become increasingly popular, commercialization of the plant has led to the emergence of products marketed as derivatives or hybrids of these species (Schwabe & McGlaughlin, 2019; de la Fuente et al., 2020; Sholler et al., 2022). Among consumers, the terms *sativa*, *indica*, and *hybrid* are used colloquially and are associated with perceived effects (McPartland, 2018). Sativa has been associated with stimulating effects, indica with sedating effects, and hybrids are perceived to be bred from the former two to fit the more personalized needs of consumers (McPartland, 2018; Piper, 2018; Schwabe & McGlaughlin, 2019; Sholler et al., 2022). Interestingly, a recent study collected data characterizing various commercial products classified as *sativa*, *indica*, or *hybrid* and used supervised and unsupervised machine learning algorithms to subjective effect tags (de la Fuente et al., 2020). The models

indicated a clear division among *sativas* and *indicas*, with *hybrids* in between, suggesting distinct subjective effects among the categories (de la Fuente et al., 2020).

Despite these perceived effects, strain categories are largely baseless (Piomelli & Russo, 2016; McPartland, 2018; Schwabe & McGlaughlin, 2019; de la Fuente et al., 2020). Instead, many researchers hold that the differences in perceived effects between strain categories may be owing to other components of cannabis (i.e., terpenes), which are rarely accurately reported to consumers (Piomelli & Russo, 2016; Booth & Bohlmann, 2019; Stasiłowicz et al., 2021; de la Fuente et al., 2022). Interestingly, some studies have found that products labeled as *indica* and *sativa* have similar concentrations of major cannabinoids but distinctly different concentrations of terpenes (Russo, 2011; Hazekamp et al., 2016; Sholler et al., 2022). To date, hundreds of different cannabinoids and terpenes have been identified, all with varying pharmacological properties and outcomes (Baron et al., 2018; Stasiłowicz et al., 2021). These cannabinoids and terpenes are also known to interact synergistically with one another to exert *entourage effects*, which can have enhanced therapeutic benefits for consumers (Baron et al., 2018; Pellati et al., 2018; Booth & Bohlmann, 2019; Russo, 2019; Stasiłowicz et al., 2021). Given this, it remains unclear whether the perceived therapeutic effects are a result of the individual components of cannabis products or the combined effects of interacting cannabinoids and terpenes. Although strain categories are largely arbitrary, many researchers continue to examine their perceived effects to better understand consumer choices (Pellati et al., 2018; Piper, 2018; Vigil et al., 2018; Stith et al., 2019; Stith et al., 2020). The nature of our data allowed us to do the same, providing insight into the naturalistic setting of

cannabis use. In essence, although the analysis of strain categories in this study provides valuable research on how efficacious various strains are perceived to be, it is worth noting that the perceived efficacy and differences between strains may be driven, at least in part, by self-selection and placebo effects.

Furthermore, previous studies have found inconsistencies between product labels and content, as well as differences in cannabinoid content reporting among labs (Vandrey et al., 2015; Jikomes & Zoorob, 2018). With recreational cannabis products, the accuracy of product labels relies heavily on growers, suppliers, and dispensaries; however, there are currently no standardized procedures or reliable methods for verifying strains or cannabis content in commercialized products (Schwabe & McGlaughlin, 2019). Despite this, consumers greatly rely on product labels for information on the cannabis content of a product, often using these labels to communicate preferences for desired effects (Piper, 2018; Schwabe & McGlaughlin, 2019; de la Fuente et al., 2020). One study even reported that demand for *indica* and *sativa* products was similar, with hypothetical purchasing tasks suggesting that consumer decisions were determined by the perceived effects of each strain in the context or setting of the typical activity-based purpose (Sholler et al., 2022). Unfortunately, because the Strainprint app prepopulates product data from multiple sources, variability across products is an issue, and we were unable to measure the accuracy of cannabinoid content for each product.

For addressing the limitations discussed above, similar future studies should investigate the effects of various terpenes and cannabinoids on perceived efficacy. Previous research has also suggested addressing strain variability by classifying cannabis

products according to chemical phenotypes and pharmacological characteristics (Russo, 2019; Schwabe & McGlaughlin, 2019; Schilling et al., 2020). A necessary next step toward accurately classifying cannabis subgroups and creating more precise product labels for consumers is a better understanding of the association between the chemical composition of individual products and the perceived effects experienced by cannabis users. As the colloquial use of strain categories is likely to persist in the commercial marketplace, it is also necessary that future studies attempt to genetically profile samples of commercialized cannabis products, such that genotypes of the same strain are at least comparable. In addition, randomized placebo-controlled trials are necessary to ultimately test the efficacy and safety of cannabis-based treatments for insomnia. Despite these limitations, this study is strengthened by its ecological validity, as data were obtained from a large naturalistic registry of medicinal cannabis users who prospectively tracked changes in their insomnia symptoms before and after cannabis use. The results of this study can help in designing future clinical trials to ultimately test the efficacy and safety profile of different cannabinoids in the management of insomnia.

3.5 Conclusion

The results of this study suggest that individuals using medicinal cannabis to manage insomnia symptoms report significant symptom reduction after use. This general perceived improvement in insomnia symptoms highlights the potential for cannabis to be used as a treatment option for sleep disorders. Future research should investigate the

benefits and harms of cannabinoids for insomnia through rigorous randomized placebo-controlled trials.

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3.7 Conflicts of Interest

JM is a principal and senior scientist in BEAM Diagnostics, Inc, and a consultant to Clairvoyant Therapeutics, Inc. The other authors have no conflicts of interest to declare.

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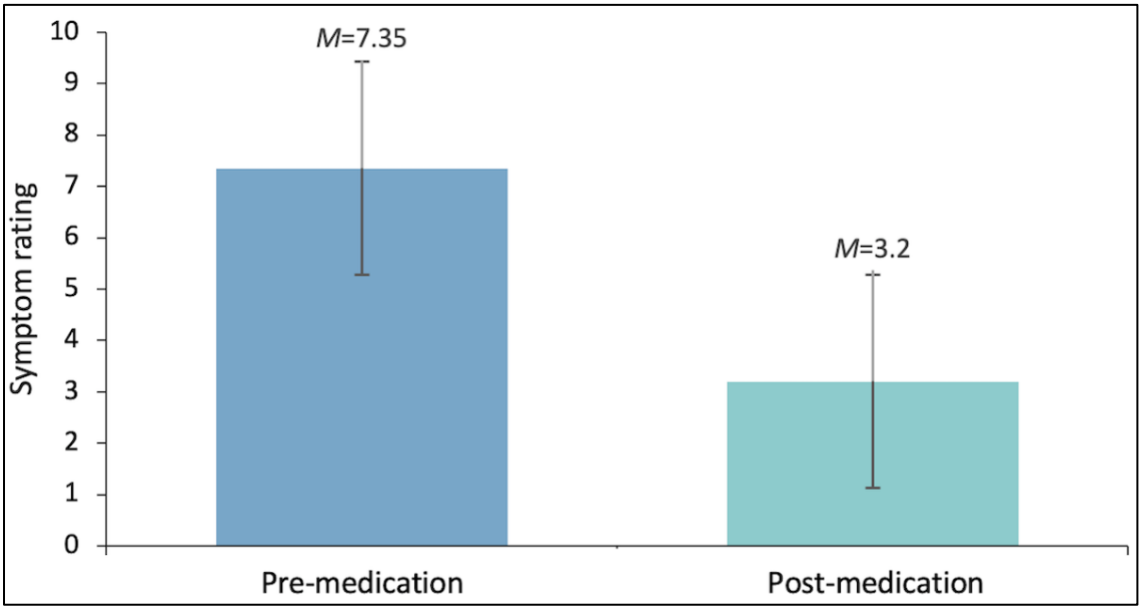
3.9 Figures and Tables

Figure 1

Symptom Severity Ratings



Note. Mean symptom severity ratings pre- (mean 7.35, SD 1.88) and post- (mean 3.20, SD 2.37) cannabis use.

Table 1

Frequency of Cannabis Strain Categories

Stain Category	Sessions, n (%)
Indica	9263 (38.29)
Indica Hybrid	6468 (26.74)
CBD[a]	3327 (13.75)
Balanced Hybrid	3068 (12.68)
Sativa	1098 (4.54)
Sativa Hybrid	605 (2.5)

[a] CBD: cannabidiol

Note. Descriptive information on frequency of strain categories used across 24,189 tracked sessions.

Table 2

Frequency of Cannabis Product Forms

Product Form	Sessions, n (%)								
	By Gender			By Age (Years)					Overall
	Female	Male	Unknown	18-24	25-34	35-44	45-54	>55	
Flower	6767 (43.82)	8517 (55.2)	160 (1.04)	1712 (11.09)	3954 (25.6)	5622 (36.4)	1934 (12.5)	1997 (12.9)	15444 (100)
Oil	5407 (70.2)	2222 (28.9)	70 (0.9)	336 (4.4)	1332 (17.3)	2401 (31.2)	1609 (20.9)	1887 (24.5)	7699 (100)
Capsule	793 (94.5)	44 (5.2)	2 (0.2)	1 (0.1)	341 (40.6)	179 (21.3)	47 (5.6)	269 (32.1)	839 (100)
Edible	121 (96)	5 (4)	0 (0)	15 (11.9)	21 (16.7)	6 (4.8)	0 (0)	73 (57.9)	126 (100)
Other	36 (44)	45 (55.6)	0 (0)	2 (2.5)	6 (7.4)	38 (46.9)	18 (22.2)	17 (21)	81 (100)

Note. Frequency and percentage of cannabis product forms used across 24,189 sessions between genders and age groups.

Table 3

Frequency of Cannabis Ingestion Methods

Ingestion Method	Sessions, n (%)								
	By Gender			By Age (Years)					Overall
	Female	Male	Unknown	18-24	25-34	35-44	45-54	>55	
Vape	3985 (46.9)	4419 (52)	91 (1.1)	719 (8.5)	1773 (20.9)	3180 (37.4)	1315 (15.5)	1389 (16.4)	8495 (100)
Oil	5277 (71.4)	2044 (27.7)	68 (0.9)	321 (4.3)	1282 (17.4)	2208 (29.9)	1570 (21.2)	1840 (24.9)	7389 (100)
Smoke	2379 (38.3)	3774 (60.7)	62 (1)	947 (15.2)	2062 (33.2)	2186 (35.2)	438 (7)	521 (8.4)	6215 (100)
Edible	546 (58.6)	383 (41.1)	3 (0.3)	37 (4)	165 (17.7)	425 (45.6)	135 (14.5)	152 (16.3)	932 (100)
Pill	635 (93.5)	44 (6.5)	0 (0)	2 (0.3)	255 (37.6)	96 (14.1)	46 (6.8)	278 (40.9)	679 (100)
Tincture	121 (77.1)	32 (20.4)	4 (2.5)	12 (7.6)	37 (23.6)	41 (26.1)	54 (34.4)	12 (7.6)	157 (100)
Spray	108 (85.7)	15 (11.9)	3 (2.3)	0 (0)	16 (12.7)	51 (40.5)	25 (19.8)	32 (25.4)	126 (100)
Other	73 (37.2)	122 (62.2)	1 (0.5)	28 (14.3)	64 (32.7)	59 (30.1)	25 (12.8)	19 (9.7)	196 (100)

Note. Frequency and percentage of cannabis ingestion methods across 24,189 sessions between genders and age groups.

Table 4

Gender Versus Efficacy

Gender	Estimate	SE	*t* test[a] (*df*)	*P* value
Female	3.4289	0.1696	26.814 (852.4)	<.001
Male	3.5282	0.1288	27.399 (868.3)	<.001

[a] Tests were two-tailed

Note. Efficacy by gender. The efficacy was tested using linear mixed modeling (β coefficient was not standardized).

Table 5

Age Versus Efficacy

Age (years)	Estimate	SE	*t* test[a] (*df*)	*P* value
18-24	3.43291	0.16118	21.298 (2073.5)	<.001
25-34	3.35234	0.11098	30.206 (1656.2)	<.001
35-44	3.72108	0.10826	34.370 (1604.7)	<.001
45-54	3.12995	0.13658	22.916 (1894.7)	<.001
>55	3.76299	0.15390	24.251 (2242.4)	<.001

[a] Tests were two-tailed

Note. Efficacy by age groups. The efficacy was tested using linear mixed modeling (β coefficient was not standardized)

Table 6

Usage Time of Day Versus Efficacy

Time of Day	**Estimate**	**SE**	***t* test[a] (*df*)**	***P* value**
Morning	3.668345	0.102629	35.744 (488.1)	<.001
Afternoon	2.754512	0.225454	12.218 (120.1)	<.001
Evening	3.369924	0.119686	28.156 (391.6)	<.001
Overnight	3.449696	0.089454	38.564 (739.5)	<.001

[a] Tests were two-tailed

Note. Efficacy by use time of day. The efficacy was tested using linear mixed modeling (β coefficient was not standardized).

Table 7

Product Form Versus Efficacy

Product Form	**Estimate**	**SE**	***t* test[a] (*df*)**	***P* value**
Capsules	3.79417	0.34792	10.9054 (25.7)	<.001
Edible	4.15951	0.56358	7.3806 (7.9)	<.001
Flower	3.43969	0.08728	39.4100 (737.0)	<.001
Oil	3.47823	0.11693	29.7470 (374.8)	<.001

[a] Tests were two-tailed

Note. Efficacy by product form. The efficacy was tested using linear mixed modeling (β coefficient was not standardized).

Table 8

Strain Category Versus Efficacy

Strain Category	**Estimate**	**SE**	***t* test[b] (*df*)**	***P* value**
Balanced hybrid	3.461359	0.112701	30.713 (300.8)	<.001
CBD[a]	3.074027	0.114947	26.743 (367.7)	<.001
Indica	3.661426	0.094507	38.742 (673.9)	<.001
Indica hybrid	3.589259	0.097939	36.648 (469.1)	<.001
Sativa	2.916945	0.163117	17.883 (86.4)	<.001
Sativa hybrid	3.470149	0.171074	20.285 (92.0)	<.001

[a] CBD: cannabidiol

[b] Tests were two-tailed

Note. Efficacy by strain categories. The efficacy was tested using linear mixed modeling (β coefficient was not standardized).

Table 9

Strain Category Efficacy Comparisons

Strain Category	Estimate	SE	*t* test[b] (*df*)	*P* value
Balanced hybrid vs. CBD[a]	0.387332	0.125752	3.080 (167.3)	.03
Indica vs. balanced hybrid	0.200067	0.107863	1.855 (208.6)	.98
Indica hybrid vs. balanced hybrid	0.127900	0.104839	1.220 (128.9)	.99
Balanced hybrid vs. sativa	0.544414	0.170767	3.188 (72.0)	.03
Sativa hybrid vs. balanced hybrid	0.008790	0.181109	0.049 (75.1)	.99
Indica vs. CBD	0.587400	0.114173	5.145 (216.2)	<.001
Indica hybrid vs. CBD	0.515232	0.115805	4.450 (197.1)	<.001
CBD vs. sativa	0.157082	0.163729	0.959 (58.6)	.99
Sativa hybrid vs. CBD	0.396122	0.181141	2.187 (82.9)	.48
Indica vs. indica hybrid	0.072168	0.083424	0.865 (183.5)	.99
Indica vs. sativa	0.744481	0.159664	4.663 (69.6)	<.001
Indica vs. sativa hybrid	0.191277	0.162713	1.176 (68.4)	.99
Indica hybrid vs. sativa	0.672314	0.164905	4.077 (73.6)	<.001
Indica hybrid vs. sativa hybrid	0.119110	0.166813	0.714 (82.5)	.99
Sativa hybrid vs. sativa	0.553204	0.201776	2.742 (65.5)	.12

[a] CBD: cannabidiol

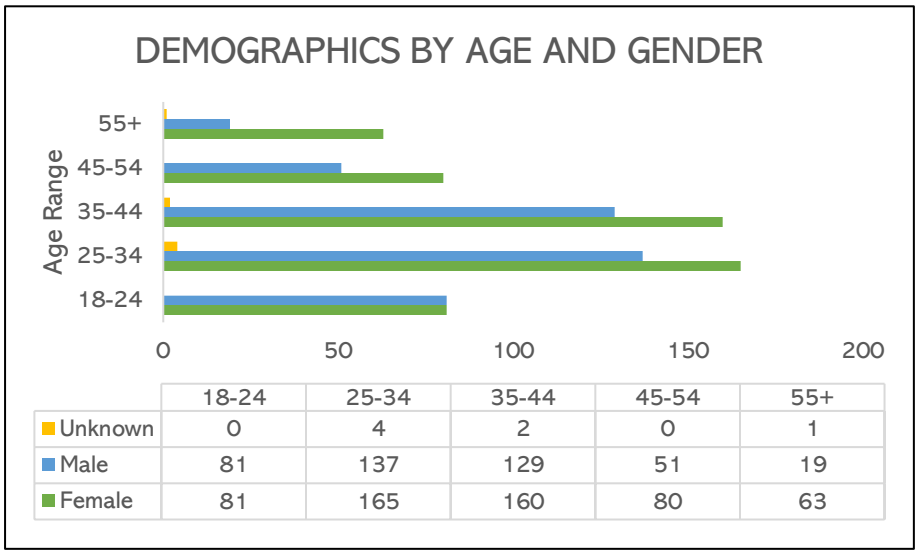
[b] Tests were two-tailed

Note. Efficacy comparisons between strain categories. The efficacy was tested using linear mixed modeling (β coefficient was not standardized)

3.10 Supplementary Material

Figure S1

Demographics By Age and Gender

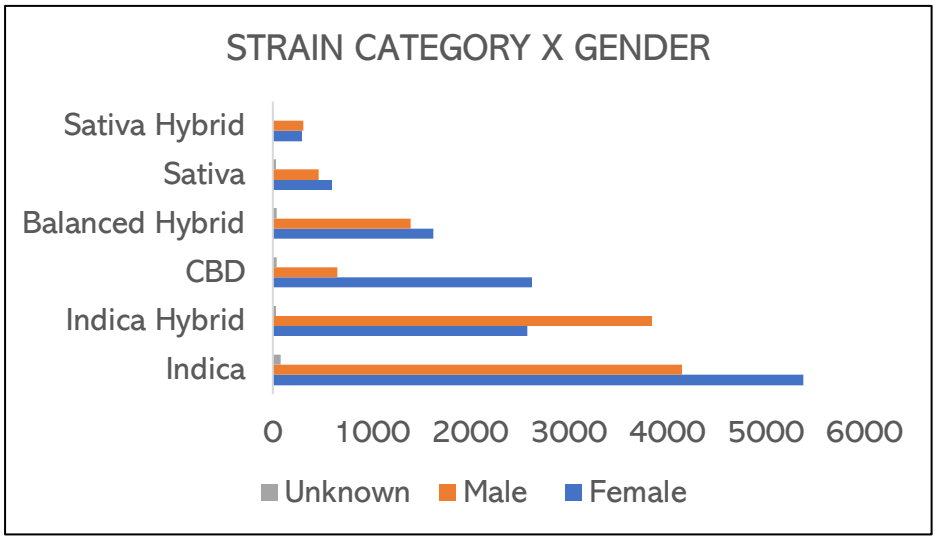


	18-24	25-34	35-44	45-54	55+
Unknown	0	4	2	0	1
Male	81	137	129	51	19
Female	81	165	160	80	63

Note. Descriptive demographic information stratified by age and gender

Figure S2

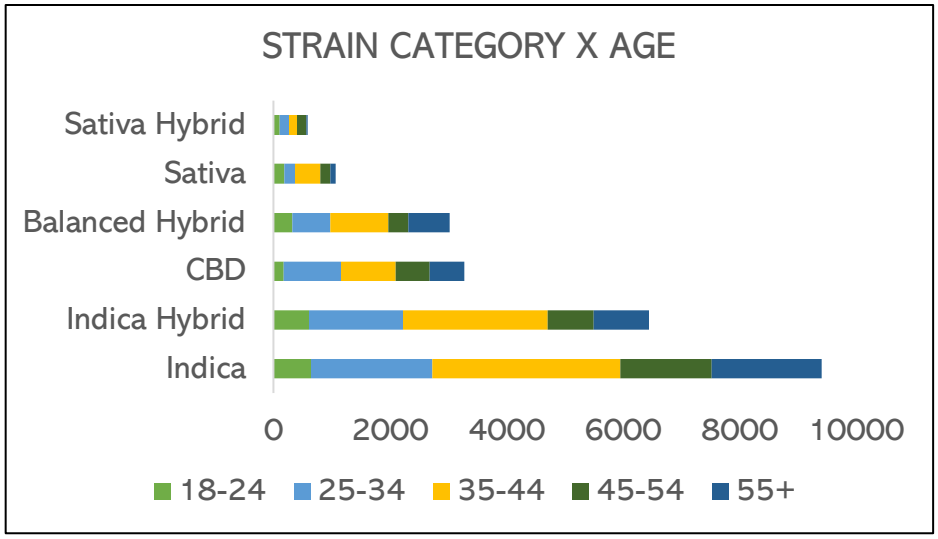
Strain Categories by Gender



Note. Descriptive information on strain categories across 24189 sessions, stratified by gender.

Figure S3

Strain Categories by Age



Note. Descriptive information on strain categories across 24189 sessions, stratified by age.

Table S1

Gender Versus Efficacy Comparisons

Gender	Estimate	SE	df	*t* value	*P* value
Male vs. Female	0.099301	0.169602	852.4	0.5855	.558

Note. Efficacy comparisons between gender. The efficacy was tested using linear mixed modeling (beta coefficient was not standardized).

Table S2

Age Versus Efficacy Comparisons

Age (years)	Estimate	SE	df	*t* value	*P* value
[18-24] vs. [25-34]	0.080574	0.164535	4505.9	0.490	1.0000
[18-24] vs. [35-44]	-0.288167	0.181906	3152.4	-1.584	1.0000
[18-24] vs. [45-54]	0.302963	0.205804	2628.0	1.472	1.0000
[18-24] vs. [55+]	-0.330076	0.218393	2732.1	-1.511	1.0000
[25-34] vs. [35-44]	-0.368740	0.117976	6311.3	-3.126	.018**
[25-34] vs. [45-54]	0.222389	0.161152	3472.9	1.380	1.0000
[25-34] vs. [55+]	-0.410650	0.177985	3541.6	-2.307	.211
[35-44] vs. [45-54]	0.591129	0.137074	5784.4	4.313	<.001***
[35-44] vs. [55+]	-0.041910	0.159343	5626.5	-0.263	1.0000
[45-54] vs. [55+]	-0.633039	0.100426	21988.3	-6.304	<.001***

Note. Efficacy comparisons between age groups. The efficacy was tested using linear mixed modeling (beta coefficient was not standardized).

Table S3

Frequency of Cannabis Product Forms

Time of Day	Sessions, n (%)
Morning	4306 (18)
Afternoon	491 (2)
Evening	5683 (23)
Overnight	13709 (57)

Note. Frequency and percentage of cannabis usage time of day across 24189 sessions.

Table S4

Product Form Versus Efficacy Comparisons

Product Form	Estimate	SE	df	*t* value	*P* value
Edible vs. Capsule	0.365348	0.651521	13.1	0.5608	1.0000
Capsule vs. Flower	0.354477	0.341137	22.8	1.0391	1.0000
Capsule vs. Oil	0.315939	0.354712	29.0	0.8907	1.0000
Edible vs. Flower	0.719824	0.558380	7.4	1.2891	1.0000
Edible vs. Oil	0.681287	0.567974	8.0	1.1995	1.0000
Oil vs. Flower	0.038537	0.107118	167.4	0.3598	1.0000

Note. Efficacy comparisons between product forms. The efficacy was tested using linear mixed modeling (beta coefficient was not standardized).

Chapter 4: An Investigation of Cannabis Use for Insomnia in Depression and Anxiety in a Naturalistic Sample

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Abstract

Background: Little is known about cannabis use for insomnia in individuals with depression, anxiety, and comorbid depression and anxiety. To develop a better understanding of distinct profiles of cannabis use for insomnia management, a retrospective cohort study was conducted on a large naturalistic sample.

Methods: Data were collected using the medicinal cannabis tracking app, Strainprint®, which allows users to monitor and track cannabis use for therapeutic purposes. The current study examined users managing insomnia symptoms in depression (n = 100), anxiety (n = 463), and comorbid depression and anxiety (n = 114), for a total of 8476 recorded sessions. Inferential analyses used linear mixed effects modeling to examine self-perceived improvement across demographic variables and cannabis product variables.

Results: Overall, cannabis was perceived to be efficacious across all groups, regardless of age and gender. Dried flower and oral oil were reported as the most used and most efficacious product forms. In the depression group, all strains were perceived to be efficacious and comparisons between strains revealed indica-dominant (M_{diff} = 1.81, 95% CI 1.26–2.36, P_{adj} < .001), indica hybrid (M_{diff} = 1.34, 95% CI 0.46–2.22, P_{adj} = .045), and sativa-dominant (M_{diff}= 1.83, 95% CI 0.68–2.99, P_{adj} = .028) strains were significantly more efficacious than CBD-dominant strains. In anxiety and comorbid conditions, all

strain categories were perceived to be efficacious with no significant differences between strains.

Conclusions: In terms of perceptions, individuals with depression, anxiety, and both conditions who use cannabis for insomnia report significant improvements in symptom severity after cannabis use. The current study highlights the need for placebo-controlled trials investigating symptom improvement and the safety of cannabinoids for sleep in individuals with mood and anxiety disorders.

Keywords

medicinal cannabis, insomnia, depression, anxiety, symptom assessment, linear mixed effects, mobile health

4.1 Introduction

Disruptions in the sleep-wake cycle are a core component of the pathophysiology of mood and anxiety disorders. Insomnia is recognized as a common sleep disorder and may present itself as a comorbidity on both symptom and/or condition levels (Morin & Benca, 2012; Levenson et al., 2015). In major depressive disorder (MDD), insomnia symptomology is reported by 80–90% of individuals, with poorer sleep associated with greater depressive symptom severity (Soehner & Harvey, 2012; Bei et al., 2018). Similarly, insomnia prevalence rates of 70–90% have been reported among individuals with anxiety disorders (Johnson et al., 2006; Soehner & Harvey, 2012), with co-occurring insomnia associated with increased risk of lifetime anxiety disorders (Johnson et al., 2006). Research on the relationship between sleep and mental illness have also reported insomnia as a post-treatment residual symptom in both mood and anxiety disorders (Hauri et al., 1974; Cervena et al., 2005; Carney et al., 2007). Despite this, evidence-based strategies for treating insomnia in mood and anxiety disorders are limited, and first-line treatments for mood and anxiety disorders do little to manage insomnia symptoms in treatment-resistant individuals (World Health Organization, 2009; Riemann et al., 2017; Bollu & Kaur, 2019).

Interest in the use of cannabis products for therapeutic purposes has grown substantially with the recent legalization of the drug in several countries. A wide range of therapeutic advantages have been reported with cannabis use, with one commonly reported benefit being its use as a sleep aid (Walsh et al., 2013). Insomnia has been described as one of the primary reasons individuals seek medicinal cannabis (Turna et al.,

2020), and approximately 1/4 of recreational users have reported that cannabis aids relaxation and sleep (Lee et al., 2007). Similar findings have also been reported regarding cannabis use for depression and anxiety (Sexton et al., 2016; Kosiba et al., 2019; Lowe et al., 2019). In fact, one study examining substitutions of medical cannabis for other pharmaceutical agents found that 71.8% of respondents reduced their use of anti-anxiety medications, 65.2% reduced their use of sleep medications, and 37.6% reduced their use of antidepressant medications with cannabis use (Piper et al., 2017). A meta-analysis of medical cannabis use reported similar findings, with anxiety (50%) and depression (34%) among the top reasons for use (Kosiba et al., 2019). Interestingly, in a retrospective study examining cannabis use for a variety of symptoms, cannabis use was also reported to provide the most relief in anxiety- and depression-related symptoms and insomnia presented the largest symptom relief score across all examined symptoms (Stith et al., 2018). Despite this, several reviews have concluded that research on the benefits of cannabis for sleep are dominated by results from studies investigating other primary conditions, with sleep as a secondary outcome (Gates et al., 2014; Babson et al., 2017; Kuhathasan et al., 2019). The present study aimed to investigate the use of cannabinoids for insomnia in individuals with depression, anxiety, and comorbid depression/anxiety and was conducted via app-based crowdsourced data from a large, naturalistic sample.

4.2 Methods

A retrospective cohort study was conducted to examine use of cannabis products for insomnia symptoms in individuals with depression and/or anxiety. All data were

anonymous and was obtained from the cannabis tracking app, Strainprint®. Using the app, subjects can record their conditions and symptoms, as well as a variety of cannabis usage variables. Of note, conditions and symptoms are subjectively determined and recorded by each individual. As such, it is possible that not all individuals meet full clinical diagnostic criteria for recorded conditions. At initial sign-up, all subjects provide consent to share their anonymized data for research purposes. Users cannot use the app or enter any data without agreeing to these terms. Once the agreement has been digitally accepted, users are prompted to enter basic demographic information. Prior to starting a session, subjects select relevant symptoms from a pre-populated dropdown list and are guided through instructions to rate the severity of their selected symptoms on a 0–10-point numeric rating scale (0-least severe; 10-very severe). Note that for the current study, we examined only insomnia symptoms in individuals with depression and/or anxiety. Next, subjects select the cannabis product they will use from a pre-populated list of products with lab-verified chemical ingredients for all medical cannabis products sold by licensed producers. Subjects then input additional information about the product and session, such as product form (flower, oil, capsule, edible, vape pen, concentrate), route of administration (vape, oil, smoke, edible, pill, tincture, spray, concentrate, dab bubble, dab portable, oral, topical, transdermal) and dose (drops, mg, ml, puffs). After an onset period defined by the selected route of administration (e.g., 20 min for smoke, 60 min for pill or edible), subjects are prompted with a push notification (occurs 8 h after initial ratings for insomnia symptoms) to complete a post-session rating of symptom severity on the same numeric scale.

The current study analyzed the data of participants who used cannabis to manage insomnia symptoms under conditions of depression and anxiety. Variables of interest were selected prior to data extraction, and Strainprint® subsequently provided all information stripped of any identifiers.

4.2.1 Ethics Approval

Ethics approval for this research was granted by the Hamilton Integrated Research Ethics Board (HiREB project #7162). The study was designed to be compliant with the Health Information Protection Act, 2016 (HIPA).

4.2.2 Study Sample

The current study included sessions tracked from February 27, 2017, to February 28, 2020. All participants in this study experienced insomnia symptomology and used the Strainprint® app to monitor and track symptom severity pre- and post- cannabis use. Participants were stratified into groups based on their self-reported condition (i.e., only depression, only anxiety, comorbid depression, and anxiety). In the depression condition, the sample consisted of 100 participants ($n = 50$ males; $n = 50$ females) tracking cannabis use across 976 recorded sessions. Participant ages ranged from 18 to 62 ($M = 30.93$, $SD = 10.07$). In the anxiety condition, 463 participants ($n = 191$ males; $n = 269$ females; $n = 3$ n/a) tracked usage across 4631 recorded sessions. Participant ages ranged from 18 to 71 ($M = 31.43$, $SD = 8.91$). Finally, in the comorbid condition, 114 participants ($n = 60$ males; $n = 54$ females) tracked usage across 2869 recorded sessions. Participant

ages ranged from 18 to 62 (M = 33.98, SD = 10.70). Additional descriptive statistics on the samples are presented in Figs. S1, S2, S3.

4.2.3 Statistical Analysis

Descriptive analyses of the data were completed for each condition. Specifically, frequencies of categorical cannabis use variables (i.e., strain category and product form) were examined. The data were further stratified to investigate cannabis usage trends across age and gender. Inferential analyses for each condition examined self-perceived symptom improvement, which was calculated as the self-reported change in symptom severity between pre- and post- cannabis use.

To ensure validity of model results, plots were examined and determined not to violate the assumptions of normality and homoscedasticity (see Appendix for more detailed information on model diagnostics). Though regression analyses are commonly conducted for statistical modelling of this type, the current data reports multiple observations per subject, violating the assumption of independent observations in standard regression models. Standard regression analyses would not account for between-person variability in tracked sessions across subjects; therefore, linear mixed effects modeling (LMEM) was applied. LMEM corrects for non-independence in data and can estimate random intercepts and slopes to make accurate inferences. LMEM uses random effects to resolve between-subject variability and standard fixed effects to resolve within-subject variability, irrespective of differences in the frequency of observations reported per subject.

For the following analyses, LMEM was applied to predict changes in self-perceived symptom improvement across demographic variables (i.e., age and gender) and cannabis use variables (i.e., product form and strain category). Each condition was examined across all tracked sessions. Bonferroni corrections for multiple comparisons were applied to all results. Analyses were conducted using the statistical computing software, R.

4.3 Results

4.3.1 Strain Categories and Product Forms

For each condition, descriptive analyses were performed across tracked sessions to examine the usage frequency of each strain category (i.e., sativa-dominant, sativa hybrid, indica-dominant, indica hybrid, balanced hybrid, cannabidiol [CBD]). Although CBD is not a plant strain, Strainprint® codes CBD-dominant products as a distinct category because of the varying amounts of THC (Δ^{9}-tetrahydrocannabinol)/CBD across different strains. Descriptive statistics examining strain categories for each condition are presented in Figs. S4, S5, S6.

The percentage frequency of each strain category for depression was examined across 976 sessions. Results indicate that CBD-dominant and indica-dominant strains were most used to manage insomnia symptoms in depression (Fig. S4). Strain category usage frequency was examined across 4631 sessions in the anxiety condition (Fig. S5) and across 2869 sessions in the comorbid condition (Fig. S6). In both anxiety and comorbid conditions, indica-dominant and indica hybrid strains were most used to

manage insomnia. Notably, across all conditions, sativa-dominant and sativa hybrid strains were least used.

Descriptive analyses of cannabis product forms (i.e., flower, oil, other) for the management of insomnia are stratified by age and gender and frequencies (Tables S1-S2, S3). Cannabis was most often used in the form of dried flower across most conditions, except in individuals between 35 and 44 years of age with depression, and in individuals 45+ years of age with anxiety or comorbid conditions, who used oil more often.

4.3.2 Linear Mixed Effects Model Predictions of Self-Perceived Symptom Improvement

Figures S7, S8, S9 present bar graphs of insomnia symptom severity ratings for each condition before and after cannabis use. Fig. S7 examines pre-medication ($M = 6.76$, $SD = 1.90$) and post-medication ($M = 3.24$, $SD = 2.87$) insomnia symptom severity across tracked sessions for the depression condition ($n = 100$ users across 976 sessions). Fig. S8 examines pre-medication ($M = 7.24$, $SD = 1.86$) and post-medication ($M = 3.61$, $SD = 2.55$) symptom severity across tracked sessions for the anxiety condition ($n = 463$ users across 4631 sessions). Finally, Fig. S9 examines pre-medication ($M = 7.10$, $SD = 2.01$) and post-medication ($M = 2.73$, $SD = 2.26$) symptom severity across tracked sessions in the comorbid condition ($n = 114$ users across 2869 sessions).

4.3.1.1 Depression

Cannabis was perceived as significantly efficacious ($P_{adj} < 0.01$) for most age groups in the depression condition (Table 1). Interestingly, cannabis was not perceived as

efficacious for the 45+ age group. There were no significant differences in self-perceived symptom improvement found between age groups (Table S4).

Self-perceived symptom improvement was also examined across various product forms and was significantly efficacious in the form of a flower or oil ($P_{adj} < 0.01$) (Table S5). Product forms with an insufficient number of observations to warrant inclusion in principal analyses (i.e., those making up < 10% of the data) were collapsed into one distinct group. Product forms of this group, consisting of capsules, edibles, vape pens, concentrates, and tinctures, were not found to be efficacious. Additional comparisons between product forms found no significant differences (Table S6).

Finally, the self-perceived symptom improvement of cannabis strain categories was examined (Table 2). All strains were perceived by the participants be efficacious improving insomnia symptoms in the depression group ($P_{adj} < 0.01$). When self-perceived symptom improvement was compared between strain categories, indica-dominant ($M_{diff} = 1.81$, 95% *CI* 1.26–2.36, $P_{adj} < .001$), indica hybrid ($M_{diff} = 1.34$, 95% *CI* 0.46–2.22, $P_{adj} = .045$), and sativa-dominant ($M_{diff} = 1.83$, 95% *CI* 0.68–2.99, $P_{adj} = .028$) strains were found to be significantly more efficacious than CBD-dominant strains (Table 3).

4.3.1.2 Anxiety

When examined as a function of age, cannabis was efficacious across all age groups in the anxiety condition ($P_{adj} < 0.01$) (Table S7), and comparisons between age

groups found cannabis to be more efficacious in the 35–44 age group over the 25–34 age group (M_{diff} = 1.07, 95% *CI* 0.46–1.67, P_{adj} = .0004) (Table 4).

When self-perceived symptom improvement was examined by product, all forms (Table S8) and strain categories (Table S9) were found to be efficacious for anxiety ($P_{adj} < 0.01$). Comparisons between product forms (Table S10) and strain categories (Table S11) found no significant differences.

4.3.1.3 Comorbid Depression and Anxiety

Finally, cannabis was perceived to be efficacious across all age groups in the comorbid group ($P_{adj} < 0.01$) (Table S12).

When self-perceived symptom improvement was examined by product form, all forms were found to be efficacious (Table S13); however, comparisons between groups found cannabis in the form of an oil to be slightly more efficacious than flower (M_{diff} = 0.51, 95% *CI* 0.14–0.87, P_{adj} = .019) and other forms (M_{diff} = 1.32, 95% *CI* 0.35–2.30, P_{adj} = .024) (Table 5). An examination of strain categories found all strains to be efficacious ($P_{adj} < 0.01$) (Table S14) with no significant differences between strains (Table S15).

4.4 Discussion

The present study was conducted to investigate cannabis use profiles and self-perceived symptom improvement for insomnia in individuals with depression, anxiety, and comorbid anxiety and depression through crowdsourced health data. Self-reported

scores before and after cannabis use indicate a significant self-perceived benefit with the use of cannabinoids for insomnia. These findings are consistent with preliminary results from clinical trials, suggesting that cannabis may be a future option for insomnia management (Sarris et al., 2020).

In our study, all cannabis strains were perceived to improve insomnia by individuals with depression, anxiety, and comorbid depression and anxiety; however, in individuals with depression, CBD-dominant products were felt to be less efficacious than indica-dominant, indica hybrid, and sativa-dominant strains to improve insomnia. This could suggest that individuals with depression have a distinct response profile to CBD for insomnia, and/or CBD might exert anxiolytic effects in individuals with anxiety and comorbid depression/anxiety, which, in turn, may improve sleep. Interestingly, previous studies have suggested that insomnia may have independent relationships with depression and anxiety (Johnson et al., 2006) and it is possible that this finding is a result of distinct pathways for the relationships between depression and insomnia, and between anxiety and insomnia, respectively. Previous research suggests that insomnia could have etiologically distinct directional associations with anxiety versus depression, supporting the hypothesis that the nature of the relationship between insomnia and mental disorders may be different depending on the comorbid condition (Johnson et al., 2006). These results are in line with the varying responses to cannabis for insomnia in anxiety versus depression in our study.

Notably, our study also compared the self-perceived efficacy of cannabis for insomnia symptoms across all age ranges. The current literature on the influence of age in

cannabis and sleep outcomes is relatively scarce. However, the function of the endocannabinoid system in circadian rhythms has been well-established and emerging evidence has highlighted its potential modulating role in the regulation of sleep within the context of aging (Hodges & Ashpole, 2019; Murillo-Rodríguez et al., 2020; Winiger et al., 2021). There are also reports of differences in the pharmacokinetics of cannabis with increased age, which may potentially influence how the drug is absorbed in older adults (Dowling et al., 2008; Ahmed et al., 2015; Hodges & Ashpole, 2019; Winiger et al., 2021). As younger adults have faster basal metabolisms, it has been theorized that differences in cannabis-related effects across age groups may be explained by the unique biological effects of aging (Mokrysz et al., 2016; Winiger et al., 2021). Furthermore, previous studies examining sleep across age has consistently reported decreases in sleep quality, shorter sleep times, and more fragmented sleep with older adults (Espiritu, 2008; Bah et al., 2019; Hodges & Ashpole, 2019). Some studies have also reported age-related variability in the presentation of symptoms of major depressive disorder, with older adults reporting more sleep-related depressive symptomology, including problems sleeping during the night and more early morning awakenings (Schaakxs et al., 2017). Though cannabis was perceived efficacious across most age groups in our study, this was not true for older adults in the depressive group.

Despite the potential benefits of cannabinoids for insomnia, research in the field lacks placebo-controlled trials that assess self-perceived symptom improvement alongside risks and harms. Though some studies suggest that administration of THC and THC-derivatives, alone or in combination with CBD may improve sleep outcomes, very few

clinical studies have objectively investigated the efficacy of cannabis for sleep using validated measures and sleep as a primary outcome (Gates et al., 2014; Babson et al., 2017; Kuhathasan et al., 2019). Large placebo-controlled trials using both objective and subjective measures of sleep parameters are warranted. Additionally, given the highly comorbid nature of depression, anxiety, and sleep disorders, placebo-controlled trials investigating the use of cannabis for the management of insomnia in these populations are encouraged.

4.4.1 Limitations

The present study has several limitations. First, reported conditions and symptoms were determined subjectively by individuals; as a result, it is unclear whether all individuals meet full diagnostic criteria for these conditions. Importantly, the lack of an objective measure of insomnia in our study is a main limitation. Although insomnia severity in the present study is measured on a 0–10-point scale, insomnia may manifest itself in different ways that were not captured with this app. Furthermore, Strainprint® collects a very specific set of information from each individual. Any additional data that may influence symptom improvement outcomes (e.g., medical history, concurrent medications, etc.) were not able to be assessed. The present study may also involve some sampling bias. As Strainprint® is largely marketed to cannabis users, resulting samples may underrepresent individuals who find cannabis to be ineffective and overrepresent those who benefit from its use. Moreover, information on potential side effects is lacking; therefore, any data regarding negative subject experiences from cannabis use are

inaccessible. Additionally, the current study examined strain categories, though differences between categories remain largely controversial (Sawler et al., 2015; Piomelli & Russo, 2016; Schwabe & McGlaughlin, 2019). Among consumers, different strains are often associated with various perceived effects (McPartland, 2018); however, many researchers maintain that any perceived effects are a result of other components of cannabis (ex. terpenes) which are not typically reported to consumers (Sawler et al., 2015; Piomelli & Russo, 2016). As such, it is possible that perceived effects reported in this study are a result of interactions between various cannabis components rather than individual strains specifically. Nonetheless, in the absence of robust RCTs, investigations of perceived effects of strain categories in naturalistic settings can improve understanding of consumer purchasing decisions (Piper, 2018), as well as inform future trial designs.

Despite its limitations, this study is strengthened by its large, naturalistic sample. Individuals were also prompted to record cannabis use in their daily environments, maximizing ecological validity of the study. As such, large mobile health studies of this sort are considerably more convenient and provide real-time information. Although in real life many people report using cannabis use for depression, anxiety and sleep, this area of research is still relatively scarce. As such, results from the naturalistic study can provide a better understanding of cannabis usage profiles for insomnia, while providing valuable information for future trials designed to evaluate efficacy and safety of cannabis for therapeutic purposes.

4.5 Conclusion

This naturalistic investigation of cannabis use for insomnia suggests that individuals with depression, anxiety, and comorbid depression and anxiety perceive benefits from using cannabis for sleep, although the extent to which this reflects pharmacological efficacy versus response expectancies (i.e., placebo effects) cannot be ascertained. In addition, compared to other cannabis strains, CBD-dominant products may be less helpful for sleep, specifically in individuals with depression. The current study highlights the need for placebo-controlled trials investigating the efficacy and safety of cannabinoids for sleep in individuals with mood and anxiety disorders.

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4.7 Competing Interests

JM is a principal in BEAM Diagnostics, Inc. and a Consultant to Clairvoyant Therapeutics, Inc. NK, LM and BNF have no competing interests to declare.

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4.9 Figures and Tables

Table 1

Depression: Age X Self-Perceived Insomnia Symptom Improvement

Age (years)	Estimate	Std. Error	df	t value	p value	Cohen's D [95% CI]
18-24	2.755	0.495	188.2	5.569	3.504e-07***	0.41 [0.26, 0.55]
25-34	2.669	0.409	93.1	6.524	1.409e-08***	0.68 [0.45, 0.90]
35-44	3.087	0.726	73.7	4.251	2.462e-04***	0.50 [0.25, 0.74]
45+	2.339	1.113	116.9	2.102	0.151	0.19 [0.01, 0.38]

***$p < .001$

Note. $N_{sessions}$ = 976; $N_{subjects}$ = 100. Self-perceived insomnia symptom improvement by age group in depression. The self-perceived symptom improvement was tested using linear mixed modeling (β coefficient was not standardized).

Table 2

Depression: Strain Category X Self-Perceived Insomnia Symptom Improvement

Strain Category	Estimate	Std. Error	df	t value	p value	Cohen's D [95% CI]
Balanced Hybrid	2.483	0.442	266.3	5.618	< 1.32e-15 ***	0.34 [0.22, 0.47]
CBD-dominant	1.498	0.410	183.8	3.657	< 1.32e-15 ***	0.27 [0.12, 0.42]
Indica-dominant	3.306	0.374	139.2	8.844	< 1.32e-15 ***	0.75 [0.56, 0.94]
Indica Hybrid	2.836	0.405	193.7	6.998	< 1.32e-15 ***	0.50 [0.35, 0.65]
Sativa-dominant	3.329	0.579	427.0	5.745	< 1.32e-15 ***	0.28 [0.18, 0.37]
Sativa Hybrid	2.699	0.702	504.2	3.843	< 1.32e-15 ***	0.17 [0.08, 0.26]

***$p < .001$

Note. $N_{sessions}$ = 976; $N_{subjects}$ = 100. Self-perceived insomnia symptom improvement by strain category in depression. The self-perceived symptom improvement was tested used linear mixed modeling (beta coefficient was not standardized).

Table 3

Depression: Strain Category Self-Perceived Insomnia Symptom Improvement Comparisons

Strain Category	**Estimate**	**Std. Error**	**df**	**t value**	**p value**	**Cohen's D [95% CI]**
Balanced Hybrid – CBD-dominant	0.985	0.426	966.3	2.312	0.315	0.07 [0.01, 0.14]
Balanced Hybrid – Indica-dominant	− 0.823	0.389	964.5	−2.116	0.519	− 0.07 [− 0.13, 0.00]
Balanced Hybrid – Indica Hybrid	− 0.353	0.446	953.9	− 0.792	1.000	−0.03 [− 0.09, 0.04]
Balanced Hybrid – Sativa-dominant	− 0.846	0.616	949.0	−1.374	1.000	−0.04 [− 0.11, 0.02]
Balanced Hybrid – Sativa Hybrid	−0.216	0.746	841.8	−0.289	1.000	−0.01 [− 0.08, 0.06]
CBD-dominant – Indica-dominant	−1.808	0.279	947.7	−6.478	2.240e-09***	−0.21 [− 0.27, − 0.15]
CBD-dominant – Indica Hybrid	−1.338	0.450	851.6	−2.974	0.045**	−0.10 [− 0.17, − 0.03]
CBD-dominant – Sativa-dominant	−1.831	0.588	931.1	−3.112	0.028**	−0.10 [− 0.17, − 0.04]
CBD-dominant – Sativa Hybrid	−1.201	0.744	780.8	−1.614	1.000	−0.06 [− 0.13, 0.01]
Indica-dominant – Indica Hybrid	0.470	0.413	836.0	1.139	1.000	0.04 [−0.03, 0.11]
Indica-dominant – Sativa-dominant	−0.023	0.550	932.7	−0.041	1.000	−0.001 [− 0.07, 0.06]
Indica-dominant – Sativa Hybrid	0.607	0.721	775.6	0.842	1.000	0.03 [−0.04, 0.10]
Indica Hybrid – Sativa-dominant	−0.493	0.614	876.2	−0.802	1.000	−0.03 [− 0.09, 0.04]
Indica Hybrid – Sativa Hybrid	0.137	0.704	845.0	0.195	1.000	0.007 [−0.06, 0.07]
Sativa-dominant – Sativa Hybrid	0.630	0.845	832.5	0.746	1.000	0.03 [−0.04, 0.09]

***$p < .001$, **$p < .01$

Note. $N_{sessions}$ = 976; $N_{subjects}$ = 100. Self-perceived insomnia symptom improvement comparisons by strain category in depression. The self-perceived symptom improvement was tested used linear mixed modeling (beta coefficient was not standardized)

Table 4

Anxiety: Age Group Self-Perceived Insomnia Symptom Improvement Comparisons

Age (years)	Estimate	Std. Error	df	t value	p value	Cohen's D [95% CI]
[18–24] – [25–34]	0.669	0.305	586.7	2.192	0.173	0.18 [0.02, 0.34]
[18–24] – [35–44]	−0.397	0.362	451.8	−1.098	1.000	−0.10 [− 0.29, 0.08]
[18–24] – [45+]	0.208	0.495	413.9	0.421	1.000	0.04 [− 0.15, 0.23]
[25–34] – [35–44]	−1.066	0.307	434.8	−3.474	0.004***	−0.33 [− 0.52,-0.14]
[25–34] – [45+]	−0.460	0.458	395.0	−1.006	1.000	−0.10 [− 0.30, 0.10]
[35–44] – [45+]	0.606	0.489	394.8	1.238	1.000	0.12 [−0.07, 0.32]

***$p < .001$

Note. $N_{sessions}$ = 4631; $N_{subjects}$ = 463. Self-perceived insomnia symptom improvement comparisons between age groups in anxiety. The self-perceived symptom improvement was tested used linear mixed modeling (beta coefficient was not standardized.

Table 5

Comorbid: Product Form Self-Perceived Insomnia Symptom Improvement Comparisons

Product Form	Estimate	Std. Error	df	t value	p value	Cohen's D [95% CI]
Flower – Oil	−0.505	0.185	2734.1	−2.731	0.019**	−0.05 [− 0.09, − 0.01]
Flower – Other	0.818	0.478	1951.1	1.711	0.262	0.04 [−0.01, 0.08]
Oil – Other	1.323	0.498	2007.7	2.658	0.024**	0.06 [0.02, 0.10]

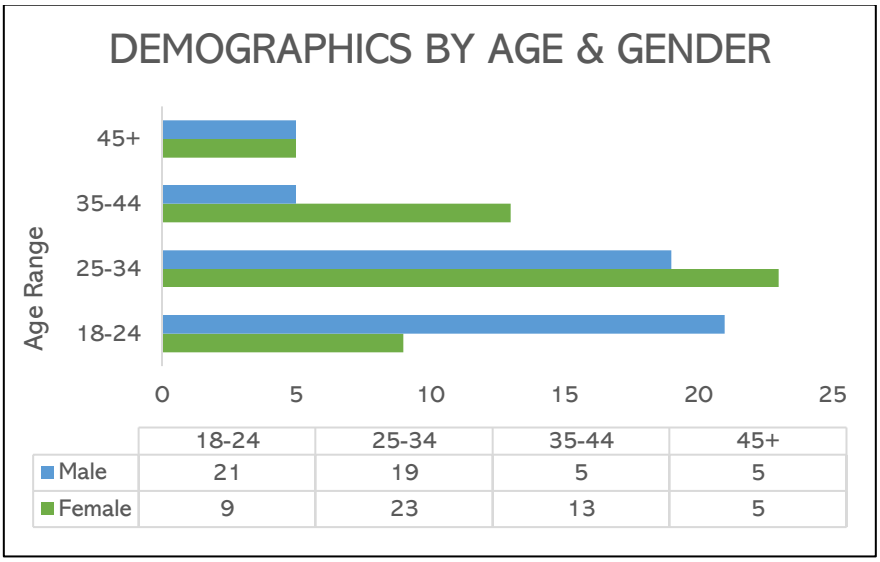
**$p < .01$

Note. $N_{sessions}$ = 2869; $N_{subjects}$ = 114. Self-perceived insomnia symptom improvement comparisons between product forms in comorbid condition. The self-perceived symptom improvement was tested using linear mixed modeling (β coefficient was not standardized).

4.10 Supplementary Material

Figure S1

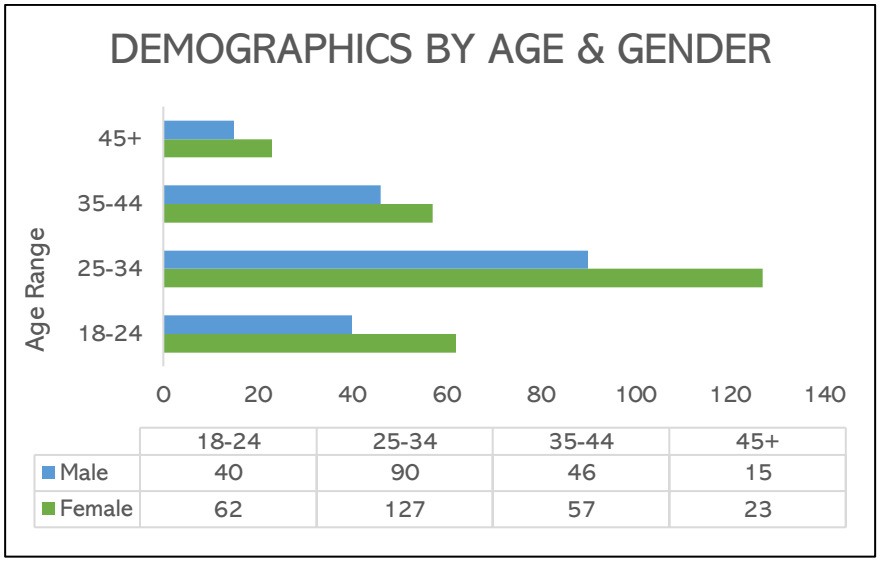
Depression: Demographics by Age and Gender



Note. Descriptive information on demographics for depression condition.

Figure S2

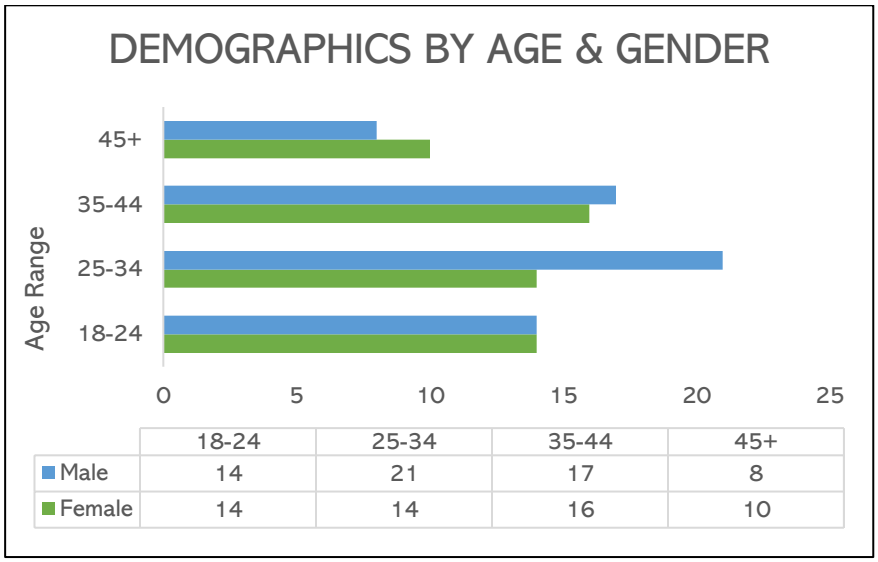
Anxiety: Demographics by Age and Gender



Note. Descriptive information on demographics for anxiety condition.

Figure S3

Comorbid: Demographics by Age and Gender

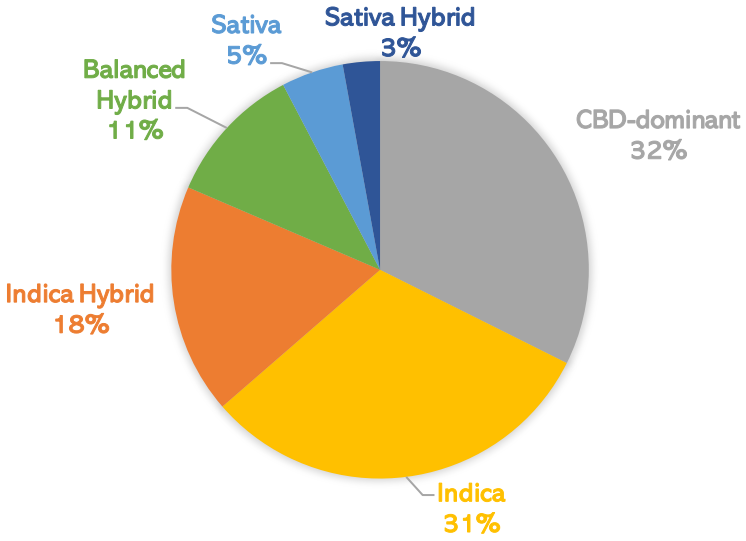


	18-24	25-34	35-44	45+
Male	14	21	17	8
Female	14	14	16	10

Note. Descriptive information on demographics for comorbid condition.

Figure S4

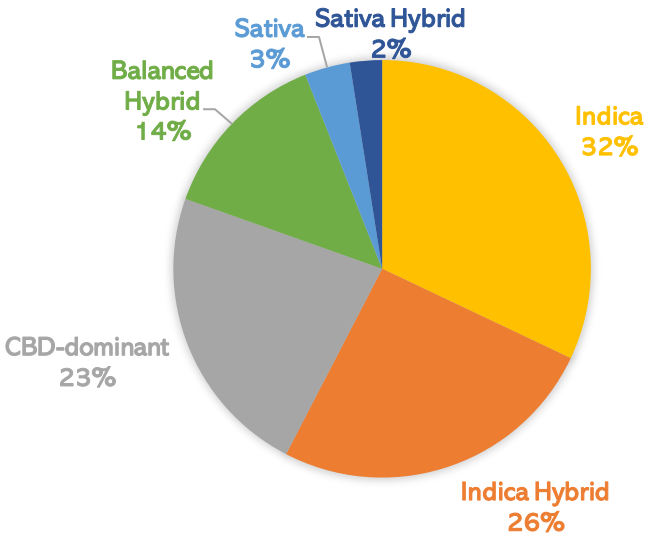
Depression: Strain Categories



Note. Descriptive information on frequency of strain categories used in depression across 976 tracked sessions.

Figure S5

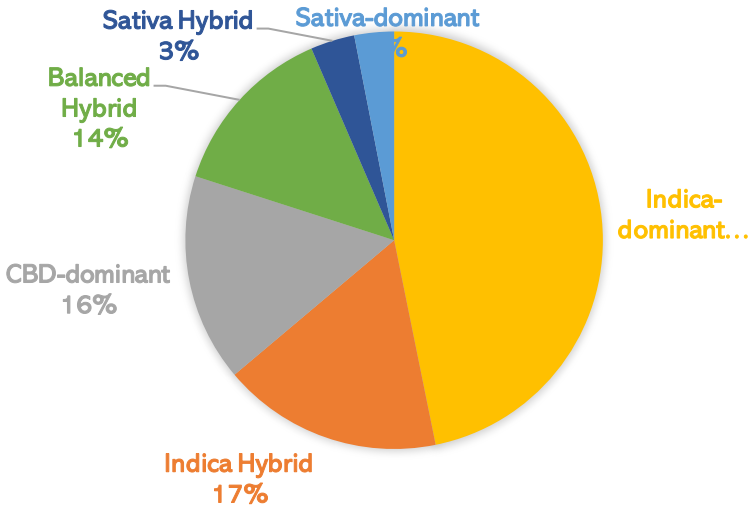
Anxiety: Strain Categories



Note. Descriptive information on frequency of strain categories used in anxiety across 4631 tracked sessions.

Figure S6

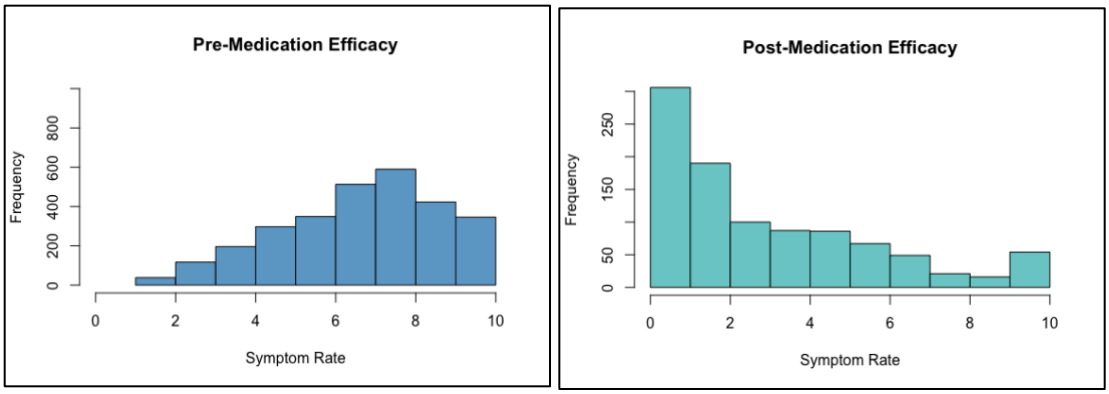
Comorbid: Strain Categories



Note. Descriptive information on frequency of strain categories used in comorbid condition across 2869 tracked sessions.

Figure S7

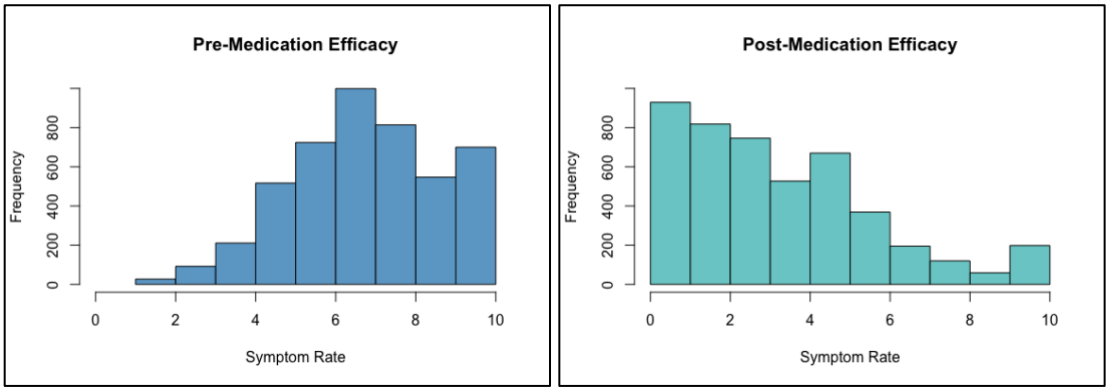
Depression: Pre- & Post-Medication Insomnia Symptom Severity



Note. Pre- (*M*=6.76, *SD*=1.90) and post-medication (*M*=3.24, *SD*=2.87) insomnia symptom severity in depression across 976 tracked sessions (n=100 users).

Figure S8

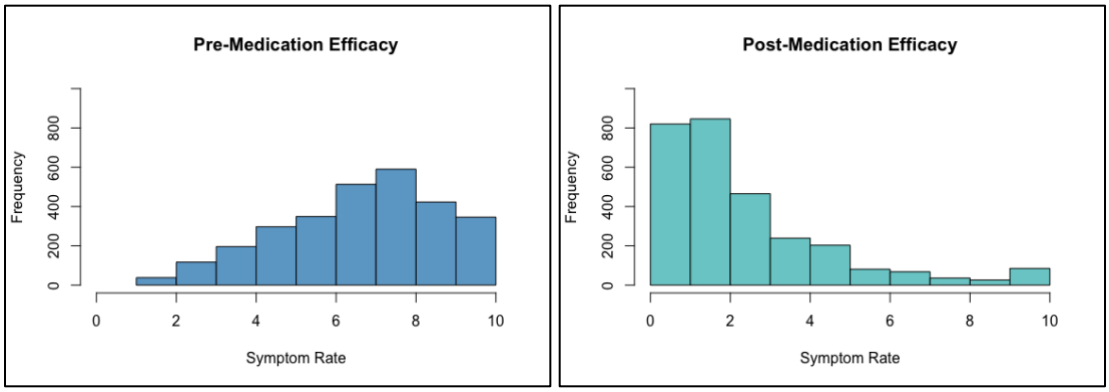
Anxiety: Pre- & Post-Medication Insomnia Symptom Severity



Note. Pre-(*M*=7.24, *SD*=1.86) and post-medication (*M*=3.61, *SD*=2.55) insomnia symptom severity in anxiety across 4631 tracked sessions (n=463 users).

Figure S9

Comorbid: Pre- & Post-Medication Insomnia Symptom Severity



Note. Pre-(*M*=7.10, *SD*=2.01) and post-medication (*M*=2.73, *SD*=2.26) insomnia symptom severity in comorbid condition across 2869 tracked sessions (n=114 users).

Table S1

Depression: Frequency of Cannabis Product Forms

Product Form	Sessions					
	By Gender		By Age (Years)			
	Female	Male	18-24	25-34	35-44	45+
Flower	285	488	81	520	127	45
Oil	171	22	2	29	154	8
Other	2	8	0	10	0	0

Note. Frequency of cannabis product forms used in depression across 976 sessions between genders and age groups

Table S2

Anxiety: Frequency of Cannabis Product Forms

Product Form	Sessions					
	By Gender		By Age (Years)			
	Female	Male	18-24	25-34	35-44	45+
Flower	1643	1548	563	1603	878	146
Oil	243	1128	369	214	283	503
Other	49	20	7	15	39	7

Note. Frequency of cannabis product forms used in anxiety across 4631 sessions between genders and age groups

Table S3

Comorbid: Frequency of Cannabis Product Forms

Product Form	Sessions					
	By Gender		By Age (Years)			
	Female	Male	18-24	25-34	35-44	45+
Flower	1245	653	270	582	988	58
Oil	346	566	61	132	268	451
Other	25	34	4	22	24	9

Note. Frequency of cannabis product forms used in comorbid condition across 2869 sessions between genders and age groups.

Table S4

Depression: Age Group Self-Perceived Insomnia Symptom Improvement Comparisons

Age (years)	Estimate	Std. Error	df	t value	p value	Cohen's D [95% CI]
[18-24] – [25-34]	0.086	0.494	507.2	0.173	1.000	0.02 [-0.16, 0.19]
[18-24] – [35-44]	-0.332	0.879	95.4	-0.378	1.000	-0.08 [-0.48, 0.32]
[18-24] – [45+]	0.416	1.218	125.6	0.341	1.000	0.06 [-0.29, 0.41]
[25-34] – [35-44]	-0.418	0.834	77.8	-0.501	1.000	-0.11 [-0.56, 0.33]
[25-34] – [45+]	0.330	1.186	113.6	0.278	1.000	0.05 [-0.32, 0.42]
[35-44] – [45+]	0.748	1.329	100.8	0.563	1.000	0.11 [-0.28, 0.50]

Note. $N_{sessions}$ = 976; $N_{subjects}$ = 100. Self-perceived insomnia symptom improvement comparisons between age groups in depression. The self-perceived symptom improvement was tested used linear mixed modeling (beta coefficient was not standardized).

Table S5

Depression: Product Form X Self-Perceived Insomnia Symptom Improvement

Product Form	Estimate	Std. Error	df	t value	p value	Cohen's D [95% CI]
Flower	2.808	0.318	85.0	8.829	3.579e-13***	0.96 [0.70, 1.21]
Oil	2.239	0.476	305.0	4.707	1.148e-05***	0.27 [0.16, 0.38]
Other	2.281	1.396	729.7	1.633	0.308	0.06 [-0.01, 0.13]

***$p < .001$

Note. $N_{sessions}$ = 976; $N_{subjects}$ = 100. Self-perceived insomnia symptom improvement by product form in depression. The self-perceived symptom improvement was tested used linear mixed modeling (beta coefficient was not standardized).

Table S6

Depression: Product Form Self-Perceived Insomnia Symptom Improvement Comparisons

Product Form	Estimate	Std. Error	df	t value	p value	Cohen's D [95% CI]
Flower – Oil	0.568	0.395	972.9	1.440	0.451	0.05 [-0.02, .11]
Flower – Other	0.527	1.380	834.8	0.382	1.000	0.01 [-0.05, 0.08]
Oil – Other	-0.041	1.431	842.8	-0.029	1.000	-0.001 [-0.07, 0.07]

Note. $N_{sessions}$ = 976; $N_{subjects}$ = 100. Self-perceived insomnia symptom improvement comparisons between product forms in depression. The self-perceived symptom improvement was tested used linear mixed modeling (beta coefficient was not standardized).

Table S7

Anxiety: Age X Self-Perceived Insomnia Symptom Improvement

Age (years)	Estimate	Std. Error	df	t value	p value	Cohen's D [95% CI]
18-24	3.216	0.259	515.7	12.406	< 8.8e-16***	0.55 [0.45, 0.64]
25-34	2.547	0.179	471.0	14.243	< 8.8e-16***	0.66 [0.56, 0.76]
35-44	3.613	0.253	391.7	14.288	< 8.8e-16***	0.72 [0.61, 0.83]
45+	3.008	0.421	382.9	7.137	1.924e-11***	0.36 [0.26, 0.47]

***$p < .001$

Note. $N_{sessions}$ = 4631; $N_{subjects}$ = 463. Self-perceived insomnia symptom improvement by age in anxiety. The self-perceived symptom improvement was tested used linear mixed modeling (beta coefficient was not standardized).

Table S8

Anxiety: Product Form X Self-Perceived Insomnia Symptom Improvement

Product Form	Estimate	Std. Error	df	t value	p value	Cohen's D [95% CI]
Flower	2.956	0.129	440.7	22.840	< 6.6e-16***	1.09 [0.97, 1.21]
Oil	3.006	0.173	1026.7	17.363	< 6.6e-16***	0.54 [0.48, 061]
Other	2.992	0.499	3207.3	5.992	6.924e-09***	0.11 [0.07, 0.14]

***$p < .001$

Note. $N_{sessions}$ = 4631; $N_{subjects}$ = 463. Self-perceived insomnia symptom improvement by product form in anxiety. The self-perceived symptom improvement was tested used linear mixed modeling (beta coefficient was not standardized).

Table S9

Anxiety: Strain Category X Self-Perceived Insomnia Symptom Improvement

Strain Category	Estimate	Std. Error	df	t value	p value	Cohen's D [95% CI]
Balanced Hybrid	2.854	0.168	1044.7	17.017	< 1.32e-15***	0.53 [0.46, 0.59]
CBD-dominant	2.882	0.166	989.7	17.347	< 1.32e-15***	0.55 [0.48, 0.62]
Indica-dominant	3.005	0.149	722.4	20.162	< 1.32e-15***	0.75 [0.67, 0.83]
Indica Hybrid	3.002	0.150	744.2	19.959	< 1.32e-15***	0.73 [0.65, 0.81]
Sativa-dominant	3.472	0.235	2625.0	14.743	< 1.32e-15***	0.29 [0.25, 0.33]
Sativa Hybrid	2.678	0.291	2985.8	9.210	< 1.32e-15***	0.17 [0.13, 0.20]

***$p < .001$

Note. $N_{sessions}$ = 4631; $N_{subjects}$ = 463. Self-perceived insomnia symptom improvement by strain category in anxiety. The self-perceived symptom improvement was tested used linear mixed modeling (beta coefficient was not standardized).

Table S10

Anxiety: Product Form Self-Perceived Insomnia Symptom Improvement Comparisons

Product Form	Estimate	Std. Error	df	t value	p value	Cohen's D [95% CI]
Flower – Oil	-0.050	0.145	4375.8	-0.346	1.000	-0.005 [-0.03, 0.02]
Flower – Other	-0.036	0.495	3682.5	-0.073	1.000	-0.001 [-0.03, 0.03]
Oil – Other	0.014	0.503	3773.3	0.028	1.000	0.0004 [-0.03, 0.03]

Note. $N_{sessions}$ = 4631; $N_{subjects}$ = 463. Self-perceived insomnia symptom improvement comparisons between product forms in anxiety. The self-perceived symptom improvement was tested used linear mixed modeling (beta coefficient was not standardized).

Table S11

Anxiety: Strain Category Self-Perceived Insomnia Symptom Improvement Comparisons

Strain Category	Estimate	Std. Error	df	t value	p value	Cohen's D [95% CI]
Balanced Hybrid – CBD-dominant	-0.028	0.165	4625.0	-0.171	1.000	-0.003 [-0.03, 0.03]
Balanced Hybrid – Indica-dominant	-0.151	0.153	4622.6	-0.990	1.000	-0.01 [-0.04, 0.01]
Balanced Hybrid – Indica Hybrid	-0.148	0.153	4625.0	-0.970	1.000	-0.01 [-0.04, 0.01]
Balanced Hybrid – Sativa-dominant	-0.618	0.238	4616.6	-2.593	0.142	-0.04 [-0.07, -0.01]
Balanced Hybrid – Sativa Hybrid	0.176	0.296	4511.7	0.594	1.000	0.009 [-0.02, 0.04]
CBD-dominant – Indica-dominant	-0.123	0.154	4577.3	-0.799	1.000	-0.01 [-0.04, 0.02]
CBD-dominant – Indica Hybrid	-0.120	0.153	4602.4	-0.783	1.000	-0.01 [-0.04, 0.02]
CBD-dominant – Sativa-dominant	-0.590	0.239	4624.6	-2.466	0.206	-0.04 [-0.07, -0.01]
CBD-dominant – Sativa Hybrid	0.204	0.298	4470.5	0.685	1.000	0.01 [-0.02, 0.04]
Indica-dominant – Indica Hybrid	0.003	0.133	4620.6	0.026	1.000	0.0004 [-0.03, 0.03]
Indica-dominant – Sativa-dominant	-0.466	0.222	4608.1	-2.098	0.540	-0.03 [-0.06, 0.00]
Indica-dominant – Sativa Hybrid	0.328	0.290	4471.0	1.13	1.000	0.02 [-0.01, 0.05]
Indica Hybrid – Sativa-dominant	-0.470	0.225	4609.7	-2.089	0.552	-0.03 [-0.06, 0.00]
Indica Hybrid – Sativa Hybrid	0.324	0.287	4509.0	1.131	1.000	0.02 [-0.01, 0.05]
Sativa-dominant – Sativa Hybrid	0.794	0.334	4600.4	2.378	0.262	0.04 [0.01, 0.06]

Note. $N_{sessions}$ = 4631; $N_{subjects}$ = 463. Self-perceived insomnia symptom improvement comparisons between strain categories in anxiety. The self-perceived symptom improvement was tested used linear mixed modeling (beta coefficient was not standardized).

Table S12

Comorbid: Age X Self-Perceived Insomnia Symptom Improvement

Age (years)	Estimate	Std. Error	df	t value	p value	Cohen's D [95% CI]
18-24	3.577	0.507	118.8	7.051	5.052e-10***	0.65 [0.45, 0.84]
25-34	2.881	0.435	126.9	6.618	3.697e-09***	0.59 [0.40, 0.77]
35-44	3.386	0.457	120.0	7.417	7.492e-11***	0.68 [0.48, 0.87]
45+	3.276	0.664	112.8	4.936	1.110e-05***	0.46 [0.27, 0.66]

***$p < .001$

Note. $N_{sessions}$ = 2869; $N_{subjects}$ = 114. Self-perceived insomnia symptom improvement by age in comorbid condition. The self-perceived symptom improvement was tested used linear mixed modeling (beta coefficient was not standardized).

Table S13

Comorbid: Product Form X Self-Perceived Insomnia Symptom Improvement

Product Form	Estimate	Std. Error	df	t value	p value	Cohen's D [95% CI]
Flower	3.189	0.258	118.5	12.374	< 6.6e-16***	1.14 [0.90, 1.37]
Oil	3.694	0.289	176.2	12.803	< 6.6e-16***	0.96 [0.78, 1.14]
Other	2.371	0.513	724.3	4.622	1.351e-05***	0.17 [0.10, 0.25]

***$p < .001$

Note. $N_{sessions}$ = 2869; $N_{subjects}$ = 114. Self-perceived insomnia symptom improvement by product form in comorbid condition. The self-perceived symptom improvement was tested used linear mixed modeling (beta coefficient was not standardized).

Table S14

Comorbid: Strain Category X Self-Perceived Insomnia Symptom Improvement

Strain Category	Estimate	Std. Error	df	t value	p value	Cohen's D [95% CI]
Balanced Hybrid	3.471	0.292	183.6	11.884	< 1.32e-15 ***	0.88 [0.71, 1.05]
CBD-dominant	3.386	0.292	183.5	11.600	< 1.32e-15 ***	0.86 [0.69, 1.02]
Indica-dominant	3.244	0.264	124.5	12.309	< 1.32e-15 ***	1.10 [0.88, 1.32]
Indica Hybrid	3.011	0.280	157.2	10.738	< 1.32e-15 ***	0.86 [0.67, 1.04]
Sativa-dominant	3.629	0.385	503.5	9.421	< 1.32e-15 ***	0.42 [0.33, 0.51]
Sativa Hybrid	2.760	0.359	409.0	7.691	6.588e-13 ***	0.38 [0.28, 0.48]

***$p < .001$

Note. $N_{sessions}$ = 2869; $N_{subjects}$ = 114. Self-perceived insomnia symptom improvement by strain category in comorbid condition. The self-perceived symptom improvement was tested used linear mixed modeling (beta coefficient was not standardized).

Table S15

Comorbid: Strain Category Self-Perceived Insomnia Symptom Improvement Comparisons

Strain Category	Estimate	Std. Error	df	t value	p value	Cohen's D [95% CI]
Balanced Hybrid – CBD-dominant	0.085	0.228	2854.6	0.372	1.000	0.007 [-0.03, 0.04]
Balanced Hybrid – Indica-dominant	0.227	0.184	2861.9	1.233	1.000	0.02 [-0.01, 0.06]
Balanced Hybrid – Indica Hybrid	0.460	0.194	2860.8	2.366	0.270	0.04 [0.01, 0.08]
Balanced Hybrid – Sativa-dominant	-0.158	0.327	2857.8	-0.481	1.000	-0.009 [-0.05, 0.03]
Balanced Hybrid – Sativa Hybrid	0.711	0.282	2807.9	2.518	0.179	0.05 [0.01, 0.08]
CBD-dominant – Indica-dominant	0.142	0.177	2860.0	0.803	1.000	0.02 [-0.02, 0.05]
CBD-dominant – Indica Hybrid	0.375	0.216	2849.8	1.734	1.000	0.03 [0.00, 0.07]
CBD-dominant – Sativa-dominant	-0.243	0.332	2860.2	-0.731	1.000	-0.01 [-0.05, 0.02]
CBD-dominant – Sativa Hybrid	0.626	0.301	2841.1	2.080	0.564	0.04 [0.00, 0.08]
Indica-dominant – Indica Hybrid	0.233	0.160	2862.8	1.454	1.000	0.03 [-0.01, 0.06]
Indica-dominant – Sativa-dominant	-0.385	0.311	2857.5	-1.238	1.000	-0.02 [-0.06, 0.01]
Indica-dominant – Sativa Hybrid	0.484	0.274	2816.6	1.770	1.000	0.03 [0.00 0.07]
Indica Hybrid – Sativa-dominant	-0.618	0.320	2858.4	-1.932	0.802	-0.04 [-0.07, 0.00]
Indica Hybrid – Sativa Hybrid	0.251	0.278	2814.0	0.901	1.000	0.02 [-0.02, 0.05]
Sativa-dominant – Sativa Hybrid	0.869	0.357	2823.8	2.436	0.224	0.05 [0.01, 0.08]

Note. $N_{sessions}$ = 2869; $N_{subjects}$ = 114. Self-perceived insomnia symptom improvement comparisons between strain categories in comorbid condition. The self-perceived symptom improvement was tested used linear mixed modeling (beta coefficient was not standardized).

Chapter 5: Predictors of Symptom Change with Cannabis Use for Mental Health Conditions in a Naturalistic Sample: A Machine Learning Approach

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The chapter in its entirety has been **submitted** to **Comprehensive Psychiatry**.

Abstract

Background: Use of cannabis for mental health conditions has been commonly reported in naturalistic field studies, despite limited clinical evidence of its efficacy. The aim of the current study was to use machine learning methods to investigate predictors of mental health symptom change with cannabis use in a large naturalistic sample.

Methods: Data from 105,052 sessions of cannabis use from 1,307 individuals using cannabis to manage mental health symptoms were analyzed. Data were extracted from Strainprint®, a mobile app that allows users to monitor their cannabis use for therapeutic purposes. Machine learning models were employed to predict self-perceived symptom change after cannabis use, and SHapley Additive exPlanations (SHAP) value plots were used to assess feature importance of individual predictors in the model. Interaction effects of symptom severity pre-scores of anxiety, depression, insomnia, and gender were also examined.

Results: The factors that were most strongly associated with symptom change following cannabis use were pre-symptom severity, age, gender, and the ratio of CBD to THC. Further examination on the impact of baseline severity for the most commonly reported symptoms revealed distinct responses to cannabis use. Responses to cannabis use also differed between genders.

Conclusions:

Findings from this study highlight the importance of several factors in predicting symptom change with cannabis use for mental health. Mental health profiles and baseline symptom severity may play a larger role in perceived responses to cannabis. Distinct response patterns were also noted across mental health conditions, emphasizing the need for placebo-controlled cannabis trials for specific user profiles.

Keywords

Machine learning, SHAP, mental health, therapeutic cannabis, gender, symptom severity

5.1 Introduction

The global trend towards cannabis legalization has led to recreational cannabis use becoming a common occurrence across a growing number of jurisdictions worldwide (Hall et al., 2019; Hammond et al., 2020; Shover & Humphreys, 2019; Windle et al., 2019). With the evolving landscape around cannabis policies, interest in understanding real-life patterns and profiles of societal cannabis use has increased (Hammond et al., 2020; MacKillop, 2019; Shover & Humphreys, 2019; Pacula et al., 2014). Beyond recreational cannabis use, use for therapeutic purposes remains understudied. Cannabis and its derivatives have frequently been used for various medical conditions, and some existing research has demonstrated its benefits for pain-related conditions (McDonagh et al., 2022; Fitzcharles et al., 2021; Johal et al., 2020; Mücke et al., 2018; Romero-Sandoval et al., 2017); however, its use in the management of mental health problems remains unclear. Despite this, mental health symptoms are consistently reported among the top reasons for therapeutic cannabis use, with self-reported depression, anxiety, and insomnia being consistently reported as the most common mental health symptoms cannabis is used for (Kosiba et al., 2019; Lintzeris et al., 2018; Sarris et al., 2020; Sexton et al., 2016; Walsh et al., 2013; Turna et al., 2020). In a large survey of 1429 medicinal cannabis users, 58% of users reported using cannabis to manage anxiety, while 58% reported using cannabis to manage depressive symptoms (Sexton et al., 2016). A similar study investigating cannabis use for therapeutic purposes found that cannabis was used to manage symptoms of pain, depression, anxiety, and sleep disturbance across several medical conditions (Walsh et al., 2013). In recent years, cannabis' popularity as a

potential therapeutic agent has also resulted in its use as a substitute for prescription medications (Corroon et al., 2017; Katzman, 2014; Kvamme et al., 2021; Lucas et al., 2019). A survey investigating cannabis substitutions found that 46% of respondents reported substituting cannabis for prescription drugs, with narcotics/opioids, anxiolytics/benzodiazepines, and antidepressants noted as the most common classes of substitutions (Corroon et al., 2017). Notably, more recent studies have also found that individuals using cannabis for therapeutic purposes often tailor their usage to specific symptoms and conditions. For example, in a recent study of 100 cannabis users recruited from a community dispensary, researchers used structured clinical interviews and standardized instruments to assess subjects for a range of psychiatric conditions (Yau et al., 2019). Although the prevalence of psychiatric illness was high in this cohort, many subjects endorsed additional psychological symptoms of mild severity and reported using cannabis to manage these symptoms. Further investigation revealed differences in cannabis formulations, ingestion methods, and frequency of use in relation to the specific symptoms and psychiatric conditions the subjects were treating (Yau et al., 2019).

As regulatory restrictions surrounding cannabis use and possession ease across several jurisdictions, in contrast with the lack of clear clinical guidelines for cannabis use in mental health conditions, there is an increased need to understand the self-perceived efficacy of cannabis products for mental health symptom management. Machine learning and big data have provided novel approaches for advancing psychiatry research (Bzdok & Meyer-Lindenberg, 2018; Iniesta et al., 2016; Koppe et al., 2020). Because of the large variability in profiles of cannabis use and the heterogeneity in cannabis use for

therapeutic purposes, analyzing and understanding the self-perceived effectiveness of cannabis to manage medical symptoms require large samples and complex methods. Machine learning methods allow us to model the associations between symptom improvement and the often highly heterogeneous usage patterns of cannabis, without an immoderate use of interaction variables and a subsequent need for much larger sample sizes. These methods allow for nonlinear pattern recognition at scale and can be used to establish meaningful relationships between numerous variables. In the present study, we used machine learning methods in a large naturalistic sample of individuals who systematically provided symptom scores before and after use of cannabinoids for the management of self-reported depression, anxiety, and insomnia to better understand therapeutic cannabis use and address existing gaps in the literature.

5.2 Methods

5.2.1 Participants and Data Collection

Individuals in the current study prospectively tracked their cannabis usage for various conditions and symptoms using the mobile cannabis tracking app, Strainprint®. Collected data remained consistent across all versions of the app between 2017-2020. All individuals in the study also met the legal age requirement for recreational cannabis use in their corresponding Canadian provinces. Data were provided by the app, stripped of all identifiers. Prior to using the app to record cannabis use, individuals are asked to provide their consent to share anonymized data for research purposes and are subsequently prompted to enter general demographic information. Once this information has been

collected, users can monitor each session of cannabis use by selecting up to three relevant symptoms to track from a pre-populated dropdown list provided by the app. Symptoms are subjectively determined by each individual and the severity of each symptom is then rated on a 0-10-point numeric scale (0-least severe; 10-very severe). The app will then prompt users to select the exact product they intend on using from a pre-populated list of lab-verified cannabis products sold by licenced producers. Individuals can also manually input additional information about the product, such as product form (i.e., flower, oil, capsule, edible, vape pen, concentrate) and method of ingestion (i.e., vape, oil, smoke, edible, pill, tincture, spray, concentrate, dab bubbler, dab portable, oral, topical, transdermal). Based on the selected method of ingestion (e.g., 20 minutes for smoke, 60 minutes for pill/edible), users are prompted to rate their symptom severity again on the same numeric scale presented earlier.

For the current study, data were collected from all individuals who used the Strainprint® app to track their cannabis use for mental health symptomatology from February 2017 to October 2020. Importantly, variables of interest were selected prior to data extraction. Table 1 presents an overview of the data and the number of observations for each mental health symptom included. Demographic analyses were conducted on the total number of unique users tracking cannabis use for mental health symptoms (n=1307) and descriptive analyses on specific cannabis use variables were conducted on the total number of unique sessions (n=52341). Notably, over 50% of all observations were comprised of individuals reporting symptoms of anxiety, depression, and/or insomnia (Table 1). The sample consisted of 772 females, 523 males and 12 users who did not

provide their gender. Users ranged in age from 18 to 71 years, with a mean age of 35 years. Additional information on demographics can be found in supplementary material.

5.2.2 Ethics Approval

This research was granted ethics approval by the Hamilton Integrated Research Ethics Board (HiREB project #12903). The study was designed to be compliant with the Health Information Protection Act, 2016 (HIPA).

5.2.3 Machine Learning Analysis

As Strainprint® data is collected from a large, nationwide sample, it is ideal for machine learning. Our analysis employed supervised machine learning methods to develop a predictive model of mental health symptom change with cannabis use. Symptom change was defined as a subjective difference in symptom severity between pre- and post- symptom ratings.

For the machine learning pipeline, data were pre-processed prior to training by splitting all tracked session observations (n=105,052 observations) into training and test sets (i.e., 70% and 30% of the data, respectively). Sessions were randomly split between training and testing following the holdout protocol based on unique users (n=1,307 users) to prevent an overestimation of predictive performance metrics by ensuring that no participant was included in both training and test sets simultaneously. An XGBoost model, a scalable tree-based method that employs boosting for model ensembles, was

used with default hyperparameters (Scikit-learn library[1]) to regress the difference between pre- and post-symptom ratings (i.e., pre-score – post-score). Although other gradient-boosting systems exist, XGBoost has several algorithm enhancements (ex. regularization to avoid overfitting) that allows models to have high predictive performance (Chen & Guestrin, 2016). Dummy variables were used to transform categorical cannabis use variables. Details on the model's performance metrics can be found in supplementary material.

5.2.4 SHapley Additive exPlanations (SHAP)

To improve the interpretation of a machine learning model's output, it is necessary to assess the importance of each feature included in the model. Although simple linear models are most often used for the sake of interpretability, they often fall short in capturing accuracy when compared to more complex models. With SHAP, each feature is assigned a value that can be used to identify which predictor variables contributed most to the model (Lundberg & Lee, 2017). In this regard, the current study opted to use SHAP values for more accurate global interpretability.

A summary plot of SHAP values was used to sort features and assess the relative relationships, positive or negative, of each predictor with symptom change. Additional dependence plots were created to highlight the effect of the three most-reported mental health symptoms (depression, insomnia, and anxiety) on the model's predicted outcome. These symptoms were selected as, together, they comprise over 50% of the data. A

[1] https://scikit-learn.org/stable/

dependence plot was also created to examine the effect of gender on the model, as this variable is often overlooked in cannabis research (Greaves & Hemsing, 2020).

5.3 Results

5.3.1 Descriptive Analyses

Descriptive analyses were completed across 52,341 unique sessions to assess the frequencies of various product forms and methods of ingestion (supplementary material). The data were further stratified by age and gender to examine potential trends across user profiles.

Results indicate that females most frequently ingested cannabis by vaping, while males most frequently ingested cannabis by smoking. Cannabis was also most frequently consumed via smoking in youth (age<25) versus older individuals. Across all unique sessions, cannabis was most frequently consumed through vaping or smoking. Regarding cannabis product forms for mental health symptoms, results indicate that cannabis was most frequently used in flower form across all ages and genders. Oil was the next most frequently used product form.

5.3.2 General Model Interpretation

SHAP values were extracted from the model to determine the contribution of each variable in the model output. These variables were then graphically presented by plotting the magnitudes of SHAP values to demonstrate the distribution of each feature on symptom improvement. Figure 1 presents a summary plot of each of these features ranked

in descending order, with each plotted point representing a single observation. The position of each point on the x-axis signifies whether the effect of the feature is associated with a higher (> 0) or lower (< 0) prediction. The colour of each point represents the value of the feature (red = high; blue = low). Thus, the combination of color and position indicate the value of the feature and how it contributes to its associated model prediction. For symptom change following cannabis use for mental health symptoms, pre-symptom ratings, the age of users, the ratio of CBD to THC, and gender were the features with the highest contributions to the model's prediction. Pre-symptom ratings are expected to be among the largest contributors to prediction, as symptom change was assessed as the difference between post- and pre-symptom ratings. As a result, pre-symptom ratings can dramatically influence model predictions, and the contribution analyses of other variables were observed as a function of pre-symptom ratings.

5.3.3 Gender SHAP Interactions

As gender is often understudied in cannabis research, a dependence plot was created to illustrate any potential effects of gender on perceived symptom change (Figure 2). The plot revealed that when pre-symptom severity is higher, males may benefit from therapeutic cannabis use more than females; however, when pre-symptom severity is lower, females are more likely to benefit from cannabis use than males.

5.3.4 Depression SHAP Interactions

Depression is among the most prevalent mental health symptoms that cannabis was used to manage. Figure 3 is a dependence plot interpreting the interaction effect of mental health pre-score and depression. The plot demonstrates that users reporting lower severity of depression before cannabis use are more likely to report benefiting from cannabis than users reporting higher severity of depression before cannabis use.

5.3.5 Insomnia SHAP Interactions

A separate dependence plot was used to clarify the interaction effect between mental health pre-score and insomnia (Figure 3). The plot illustrates an effect contrasting that of depression. Users recording low initial insomnia severity are less likely than users recording high initial insomnia severity to report perceived symptom improvement following cannabis use.

5.3.6 Anxiety SHAP Interactions

Finally, Figure 3 presents a dependence plot to assess the interaction effect between mental health pre-score and anxiety. Unlike depression and insomnia, the role of pre-score on changes in anxiety is less consistent. In the case of anxiety, only the users reporting the highest anxiety pre-score appear to report benefitting from cannabis use more than users reporting lower rates of baseline anxiety severity.

5.4 Discussion

The current study used machine learning methods to investigate self-perceived symptom change with cannabis use for the management of the most common mental health reasons people use cannabis for: depression, anxiety, and insomnia. We used SHAP values to elucidate the relationships between the main predictors of symptom change. Self-reported symptom change has repeatedly been shown to be closely linked to baseline symptom severity across several mental health conditions. Our own findings also revealed pre-symptom severity to be the strongest predictor of symptom change. Covered extensively in previous literature, baseline symptom severity is one of the most robust predictors of treatment outcomes in depression (de Vries et al., 2016; Friedman et al., 2012; Khan et al., 2002), though similar associations have not been reported in anxiety disorders (de Vries et al., 2016). In line with our own research, previous studies have also reported that patients with severe depression are less likely to benefit from treatments and/or achieve remission (de Vries et al., 2016; Friedman et al., 2012). Together, these findings might suggest potential differences across conditions in the impact of pre-symptom severity on both treatment outcomes and symptom improvement.

In addition to pre-symptom severity, the features with the highest contribution to our model were age, gender, and CBD to THC ratio. Interestingly, these features are often among the least explored in cannabis literature (Greaves & Hemsing, 2020; Grotenhermen, 2012; Mauro et al., 2018; Procaccia et al., 2022). As gender is especially understudied, we created a dependence plot to illustrate any potential effects of gender on our model. We found that males and females had contrasting trends in symptom

improvement that seemed to be dependent on baseline (pre-cannabis use) symptom severity. Although the current study examines self-reported gender rather than sex, it is possible that these terms were interpreted as interchangeable by users. In this case, differences in observed gender trends may have been a result of potential sex-dependent effects of cannabis. Previous studies have reported that relative to men, women may be more sensitive to the effects of cannabis because of an increased availability of CB1 receptors (Cooper & Craft, 2018). Furthermore, although the role of reproductive hormones in cannabis research is less understood, there is an extensive body of work in mental health research demonstrating increased prevalence of depression, anxiety, and insomnia in women during reproductive years (Handy et al., 2022; Kuehner & Nayman, 2021; Le et al., 2020; Yum et al., 2019). Taken together, these findings highlight the importance of analyzing sex- and gender-dependent effects on symptom improvement with cannabis use in future studies.

Among psychiatric conditions, self-reported depression, anxiety, and insomnia are consistently among the most common reasons for cannabis use (Kosiba et al., 2019; Lintzeris et al., 2018; Sarris et al., 2020; Sexton et al., 2016; Walsh et al., 2013). This is evident in our own sample, as these symptoms comprised over 50% of the reported observations. Interestingly, although some level of improvement in severity was reported with cannabis use across all symptoms, distinct presentations of improvement were noted with each individual symptom. For example, depression and insomnia revealed converse trends. Users reporting lower depression pre-scores were predicted to report symptom improvement after cannabis use, while users who reported higher depression pre-scores

were predicted to report *worsening* symptoms after cannabis use. In contrast, users reporting lower insomnia pre-scores were predicted to report very little to no symptom improvement after cannabis use, while users reporting higher insomnia pre-scores were predicted to report benefitting from cannabis use. In anxiety, the role of pre-score severity was less consistent. In agreement with existing literature, these findings reflect the potential symptom-specific nature of cannabis therapeutics for mental health management (Fernández-Ruiz et al., 2020; MacCallum & Russo, 2018). Moreover, findings from the current study provide additional rationale for future studies investigating specific symptom profiles within diagnosed mental health conditions.

5.5 Limitations

The current study's results should be interpreted cautiously. Firstly, it is important to note that the nature of how data is collected by Strainprint® may lend itself to some criticism. Users of the app input and rate symptoms as they subjectively perceive them. Moreover, general audiences may consider many of the mental health symptoms presented by the app as interchangeable with clinical conditions (e.g., depression, anxiety, insomnia, etc.), further complicating how the symptoms may have been understood by each user. As such, symptoms may not have been interpreted as they are clinically defined, since the symptoms/conditions by which individuals reported using cannabis for may or may not be severe enough to meet a formal clinical diagnosis. Furthermore, data collected from the app is limited and additional factors that may have also influenced symptom change (ex. user lifestyle, medical history, concurrent medications, comorbid

clinical conditions, etc.) could not be evaluated. Finally, the app's platform is primarily marketed toward regular cannabis users. Since cannabis-naïve users may have been less represented in the sample, an overrepresentation of users reporting symptom improvement with cannabis use may have also been present.

In addition to the limitations discussed above, the current study also could not examine more detailed cannabis product content. Although our SHAP summary plot (Figure 1) revealed that the ratio of CBD to THC had a high contribution to our model's prediction, we could not investigate this variable further, as additional data on the products (e.g., potency, terpenes, and other phytocannabinoids) were unavailable. These individual components have also been reported to influence the perceived effects of cannabis use (Booth & Bohlmann, 2019; Nuutinen, 2018; Russo, 2011). Previous research has also reported differences in cannabinoid content reporting between labs and additional inconsistencies in product labels (Jikomes & Zoorob, 2018; Vandrey et al., 2015). Research addressing these specific limitations and cannabis constituents will be a necessary next step in understanding how the individual components of the plant may be more or less useful in the management of mental health symptoms.

Results from this study should also be interpreted alongside some methodological considerations. Importantly, SHAP analyses are only used to explain models and cannot definitively imply causality between predictors and target variables. This should also be acknowledged when interpreting dependence plots. Notably, the model generated for the current study includes the aggregated data of all mental health symptoms collected by Strainprint®. As such, it is possible that even in presented dependence plots, effects

driven by specific symptoms may be masked in the aggregated data. Future studies should generate models that can address these symptoms individually for a better understanding of distinctive symptom profiles and trends in perceived symptom change.

Notwithstanding its limitations, the current study is foundational in providing critical information on how various cannabis use-related factors may contribute to perceived symptom change in individuals managing mental health conditions in the real-world. Moreover, as machine learning requires fairly large sample sizes to make accurate predictions, the large-scale nationwide data collected by the Strainprint® app makes for a useful database for the methods employed in the study. This study is further strengthened by its naturalistic conditions. The mobile nature of data collection allowed users to record their cannabis use in their own routine environments, maximizing user convenience and ecological validity.

5.6 Conclusion

Despite an increased global interest in both medicinal and recreational cannabis legalization, research in cannabis use for mental health remains in its infancy. Although some evidence from the literature supports the therapeutic use of specific pharmaceutical cannabis formulations for somatic conditions such as pain, less is known about the potential benefits and associated risks of cannabis for specific mental health problems. The current study highlights a need for additional research in this area, with findings revealing a central role of user profiles and baseline symptom severity on therapeutic outcomes of cannabis use for mental health. Future studies should also closely examine

cannabis response patterns across mental health conditions, as the results of the current study point to distinct differences in the impact of gender, baseline severity and CBD to THC ratio on mental health symptom change.

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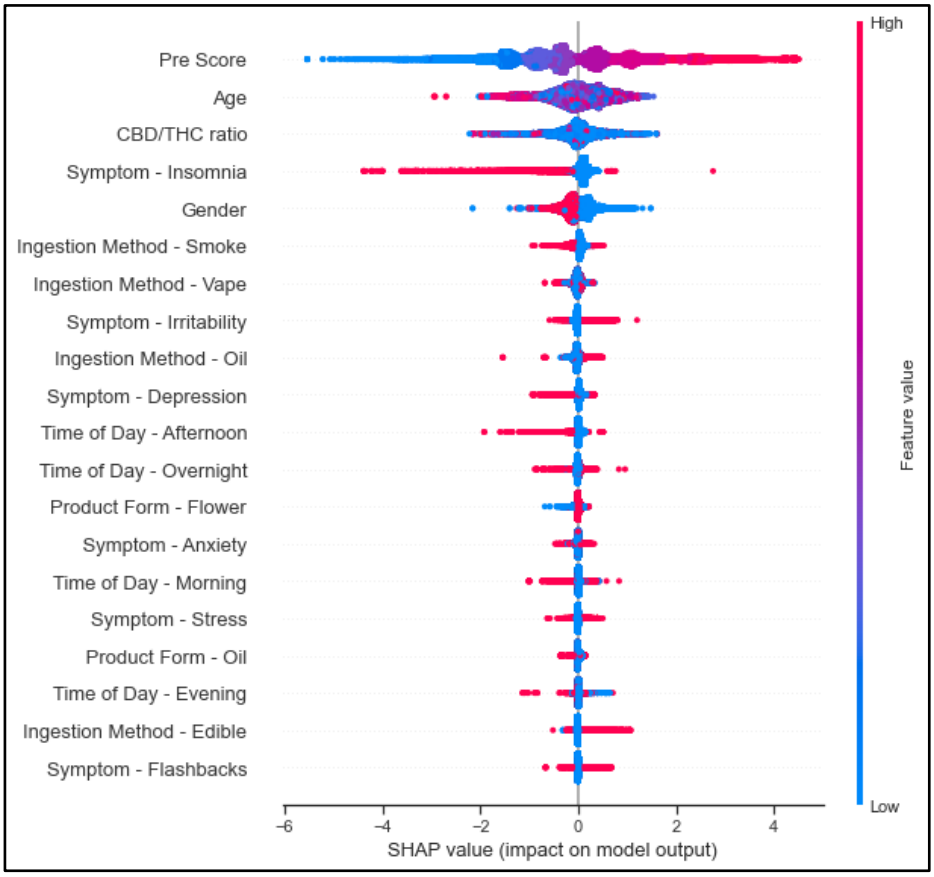
5.9 Figures and Tables

Figure 1

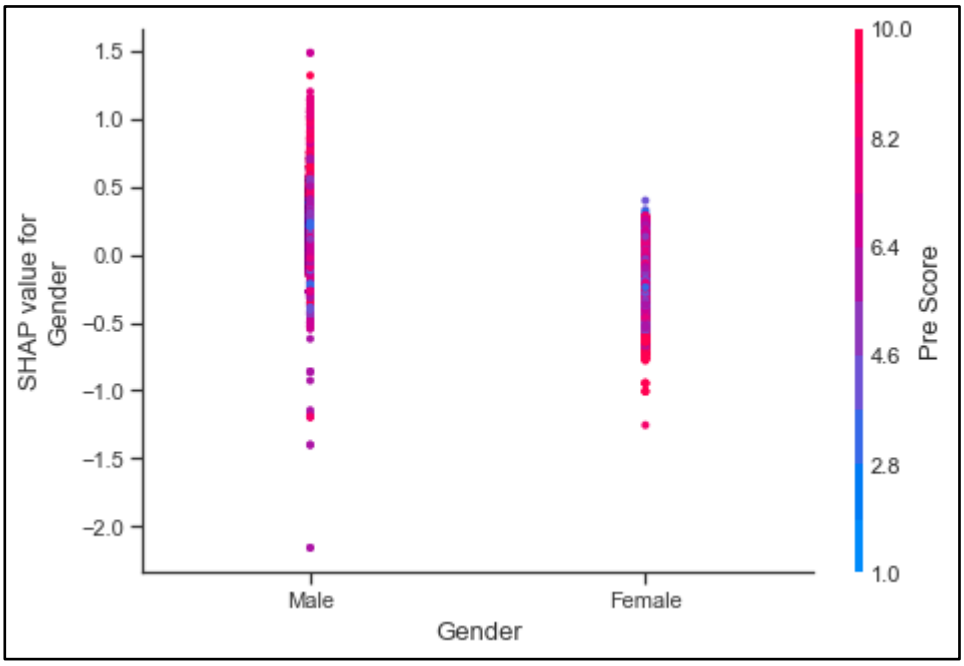
SHapley Additive exPlanations (SHAP) Feature Importance Plot



Note. SHAP summary plot of features included in the machine learning model, ranked by descending order. The position of each point on the x-axis signifies whether the effect of the feature is associated with a higher (> 0) or lower (< 0) prediction. The colour of each point signifies the original value of the feature (red = high; blue = low). Thus, the combination of position and colour indicate the value of the feature and how it contributes to its associated model prediction.

Figure 2

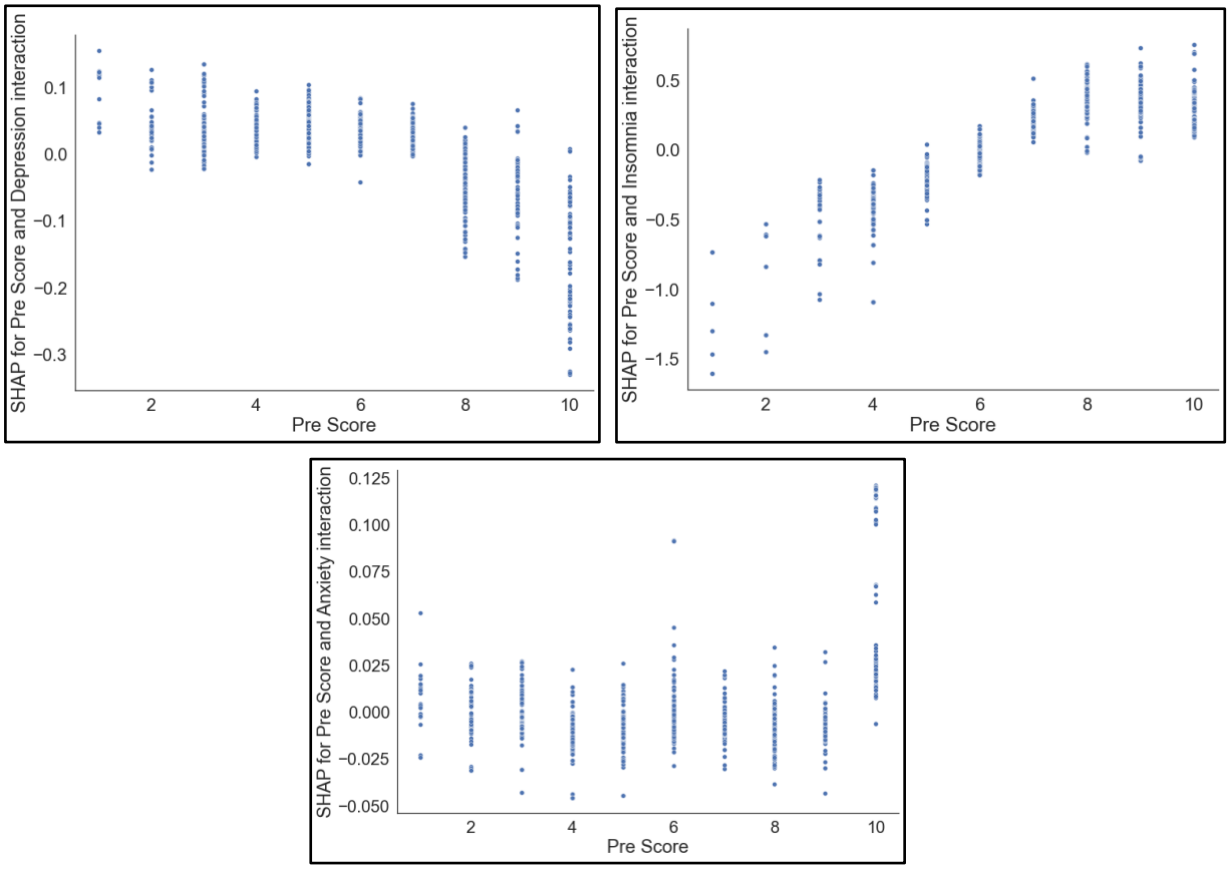
SHAP Interaction Plot for Gender



Note. SHAP interaction plot for gender. The plot demonstrates that males benefit more from cannabis use than females when pre-symptom severity is higher. When pre-symptom severity is lower, females benefit more from cannabis use than males.

Figure 3

SHAP Interaction Plots for Most Observed Symptoms



Note. SHAP interaction plots for depression, insomnia, and anxiety. Users with lower depression pre-symptom severity are more likely to benefit from cannabis use than users with higher pre-symptom severity of depression. Users with lower insomnia pre-symptom severity are less likely to benefit from cannabis use than users with higher pre-symptom severity of insomnia. No consistent pattern of symptom improvement is observed in users with anxiety.

Table 1

Overview of Observations

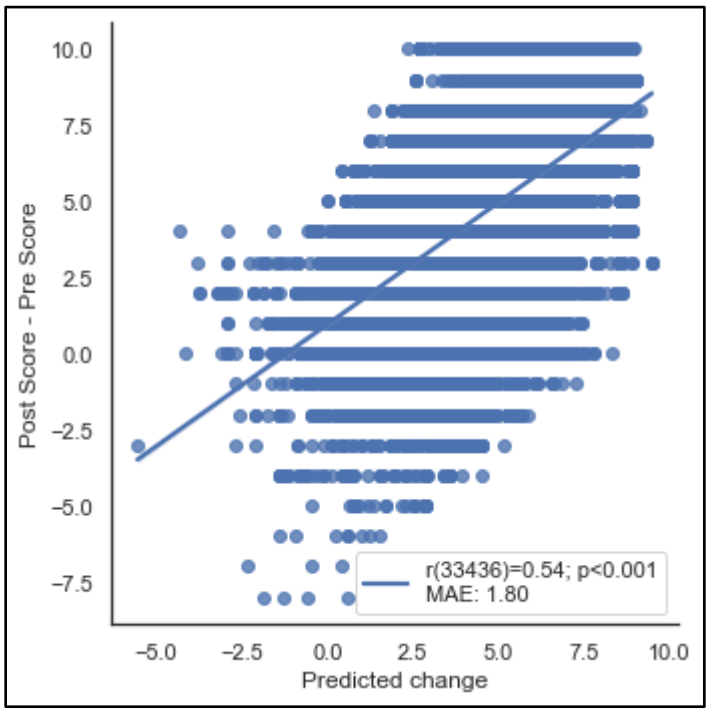
Mental Health Symptoms	**Number of Observations**
Anxiety	28224 (27%)
Insomnia	19693 (19%)
Depression	17660 (17%)
Irritability	12755 (12%)
Stress	11203 (11%)
PTSD – Flashbacks	6066 (6%)
Intrusive Thoughts	3396 (3%)
Challenge Concentrating	3225 (3%)
PMS	1278 (1%)
Compulsive Behaviour	970 (<1%)
Withdrawal	582 (<1%)
Total	**105052**

Note. Overview of the mental health symptoms observed and the frequency of each.

5.10 Supplementary Material

Figure S1

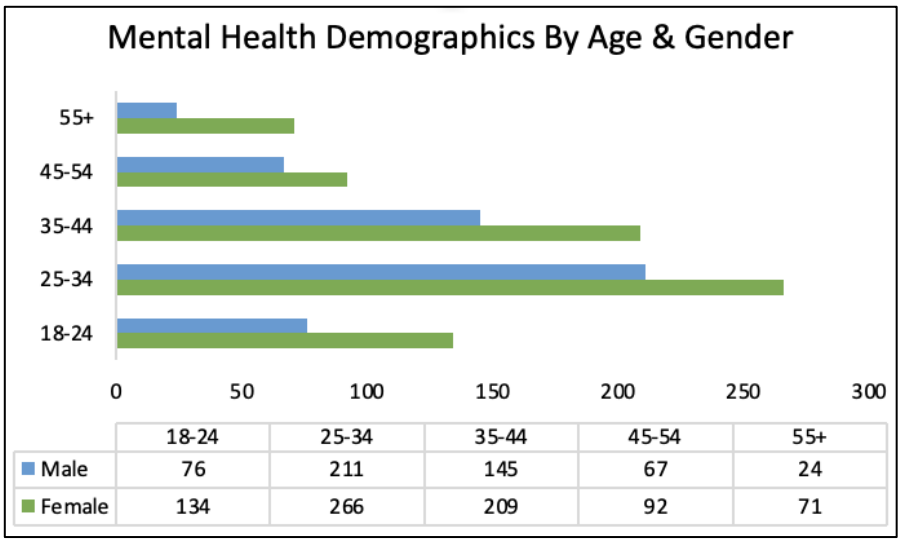
Model Performance Metrics



Note. Model performance metrics demonstrated satisfactory results (MAE = 1.8).

Figure S2

Demographic Information by Age & Gender



	18-24	25-34	35-44	45-54	55+
Male	76	211	145	67	24
Female	134	266	209	92	71

Note. Demographic information for n=1307 unique users. The total sample consisted of 772 females, 523 males. Users ranged in age from 18 to 71 with a mean age of 35.

Table S1

Frequencies of Cannabis Product Forms

Product Form	Sessions							
	Total	By Gender		By Age (Years)				
		Female	Male	18-24	25-34	35-44	45-54	55+
Flower	39215	20468	18476	3088	16429	11784	4759	3155
Oil	12245	8463	3709	565	4226	2893	2781	1780
Capsule	665	508	155	52	342	151	102	18
Edible	198	172	26	49	39	39	8	63
Vape Pen	16	15	1	2	11	3	0	0
Topical	2	2	0	0	0	1	0	1

Note. Frequency of cannabis product forms used across 52341 unique sessions between genders and age groups. Both females and males most frequently used cannabis in flower form. In youth (age <25), cannabis was also most frequently used in flower form. Across all unique sessions, cannabis was most frequently used in flower form for mental health.

Table S2

Frequencies of Cannabis Methods of Ingestion

Ingestion Method	Sessions							
	Total	By Gender		By Age (Years)				
		Female	Male	18-24	25-34	35-44	45+	55+
Vape	19048	10081	8783	652	7527	6442	2669	1759
Smoke	18901	9910	8921	2388	8535	4662	2014	1302
Oil	10940	7654	3205	492	3411	2658	2638	1741
Edible	1408	681	722	86	348	783	61	130
Tincture	614	182	428	35	468	17	80	14
Spray	592	568	24	14	352	139	50	37
Pill	555	402	151	56	248	154	82	15
Concentrate	149	110	39	6	115	8	7	13
Dab Portable	84	25	59	2	28	4	49	1
Dab Bubbler	39	7	32	21	14	2	1	1
Topical	6	5	1	3	1	0	0	2
Suppository	3	1	2	1	0	2	0	0
Transdermal	2	2	0	0	0	0	0	2

Note. Frequency of cannabis ingestion methods used across 52341 unique sessions between genders and age groups. Females most frequently ingested cannabis by vaping, while males most frequently ingested cannabis by smoking. In youth (age <25), cannabis was most frequently ingested through smoking. Across all unique sessions, cannabis was most frequently ingested for mental health through vaping or smoking.

Chapter 6: Discussion

6.1 Summary of Findings

The global shift toward cannabis legalization has highlighted its therapeutic potential for many distinct medical conditions. As the ECS is involved in several neurobiological processes, some research suggests that its dysregulation may contribute to the pathophysiology of psychiatric disorders (Mechoulam & Parker, 2013; Lowe et al., 2019; Navarrete et al., 2020; Fernández-Ruiz et al., 2020). To this extent, pharmacological manipulation of the ECS may offer promising possibilities for the development of new cannabinoid-based treatments for mental disorders. Although interest in the therapeutic properties of cannabis has increased in recent years, research on its potential applications in psychiatric disorders is nascent. Despite this, cannabis products have frequently been used to manage various mental health conditions (Walsh et al., 2013; Piper et al., 2017; Kosiba et al., 2019). As global restrictions around cannabis access ease, understanding the perceived effects of therapeutic use has become a major research priority (MacKillop, 2019). The studies included in this work explore some of the perceived therapeutic effects of cannabis for mental health and improve our understanding of how cannabinoids may be used as a tool for symptom management.

Our critical review covered in Chapter 2, examined the effects of various cannabinoid formulations on subjective and objective measures of sleep, and further assessed the quality of individual randomized controlled trials that used cannabinoid interventions. Overall, many of the studies we reviewed suggested improvements in sleep

quality and decreases in sleep disturbances; however, we noted limitations in sample sizes and the measures used to assess sleep outcomes. Importantly, we found that many of the studies we reviewed only examined sleep as a secondary outcome, highlighting the need for additional research with primary sleep outcomes.

Following federal cannabis legalization in Canada, we conducted a retrospective study to investigate cannabis use and its perceived efficacy in individuals managing insomnia. Data were collected from a nationwide sample of individuals using a mobile app to track their therapeutic cannabis use. The app allowed users to monitor symptoms before and after use by recording perceived symptom ratings on a standard Likert scale. Individuals were also able to share demographic information, and report additional data related to cannabis use such as product form, ingestion method, and cannabis strain. As discussed in chapter 3, we observed significant overall improvements in insomnia symptom ratings after cannabis use. We also noted that flowers and oils were the most used cannabis product forms in this sample. Interestingly, further analyses of reported strains revealed indica and indica hybrid-dominant strains to be more efficacious than CBD and sativa-dominant strains for insomnia management.

Building on the findings of our first study, we conducted a subsequent study to investigate cannabis use for the management of insomnia symptoms in individuals with depression, anxiety, and a comorbid presentation of the two conditions. Previous research has established that sleep difficulties are commonly reported in individuals with mood and anxiety disorders (Krystal, 2012; Khurshid, 2018; Hombali et al., 2019; Palagini et al., 2022). Several studies have also reported that insomnia is a commonly reported

residual symptom in these disorders (Soehner & Harvey, 2012; Xiao et al., 2018; Palagini et al., 2022). In the context of therapeutic cannabis use, sleep, depression, and anxiety are also among the primary reasons for use (Walsh et al., 2013; Sexton et al., 2016; Piper et al., 2017; Kosiba et al., 2019). These links are explored further in chapter 4. We applied the same methods described in our first study to assess the new sample and observed cannabis to be generally efficacious across all conditions; however, additional examination of the perceived effects of specific strains revealed differences between conditions. Notably, CBD-dominant strains were perceived to be significantly less efficacious for managing insomnia symptoms in depression than indica, indica hybrid, and sativa-dominant strains. In contrast, there were no differences noted between strains for insomnia symptom management in the anxiety and comorbid conditions.

Finally, we conclude with a study that used machine learning methods to investigate predictors of symptom change following therapeutic cannabis use. The study, presented in chapter 5, examined a large sample of individuals who used cannabis to manage common mental health symptoms. Data for this study were collected using the same mobile app described in our previous studies, but we extended our population of focus to include individuals reporting any mental health symptoms. This approach allowed us to develop broader conclusions about predictors of cannabis-based mental health symptom change. To improve the interpretability of our output, we used SHAP value plots to assess the relative contribution of each predictor to our model. Our findings revealed that the predictors most strongly associated with symptom changes were pre-symptom severity, age, gender, and the ratio of CBD to THC in cannabis products.

Descriptive analyses also revealed that depression, anxiety, and insomnia were the most reported symptoms in the sample. Given our previous research on these conditions, and the contribution of pre-symptom severity on cannabis response, we explored how the interactions of these factors influenced symptom change following cannabis use. Again, our findings revealed distinct differences in cannabis response for each of the conditions we observed.

Across our studies, we focused on cannabis use for the management of depression, anxiety, and insomnia, as they are consistently reported among the most common mental health related concerns. Though our research illustrates some therapeutic benefits with cannabis use for sleep and mental health, sample bias, the retrospective nature of our data, and the lack of robust clinical trials in this area does not allow for firm conclusions regarding cannabis efficacy. The potential undisclosed side effects also raise concerns around safety. Thus, our work underscores the need for future trials investigating the safety and efficacy of cannabinoids for sleep and mental health.

6.2 Significance of Overall Findings

The significance of the studies included in this thesis are comprehensively described in the relevant chapters. Although additional research is warranted, the results of our studies are encouraging, and serve as an important first step toward understanding perceived symptom-improvement following cannabis use for mental health management. These preliminary findings further support the exploration of the endocannabinoid system as a target for the development of future psychiatric treatments.

The concept of sleep is extensively covered in this thesis because of its interface with many psychiatric disorders. In particular, insomnia is often observed in conjunction with other mental health conditions as either a comorbid diagnosis or a related psychiatric symptom (Khurshid, 2018; Freeman et al., 2020; Palagini et al., 2022). We examined the use of cannabis for sleep disturbances across chapters 2-5, noting some positive effects for insomnia symptoms in our original research studies. Notably, in chapter 5, we observed that individuals who reported higher baseline insomnia severity were more likely to report perceived symptom improvement following cannabis use than users who reported lower baseline insomnia severity. This finding is in line with previous research that has explored treatment outcomes alongside insomnia severity. In a study investigating cognitive behavioural therapy for insomnia (CBT-I), alone or with medication, patients with shorter sleep duration at baseline demonstrated significantly more improvement in subjective sleep than those with normal sleep duration (Rochefort et al., 2019). Recent research has proposed that baseline measures of sleep may even point to different phenotypes of insomnia (Vgontzas et al., 2013; Rochefort et al., 2019). Specifically, it has been theorized that insomnia with shorter baseline sleep-duration, may be associated with a more severe profile of the disorder (Vgontzas et al., 2013; Rochefort et al., 2019). As this hypothesized phenotype is thought to be biologically rooted, individuals presenting with it are predicted to respond more favourably to pharmacological therapies that can reduce physiological arousal, than to standard psychological therapies such as behavioural interventions (Rochefort et al., 2019). In the context of cannabis use, the neuromodulatory role of the ECS is thought to significantly

contribute to sleep homeostasis (Murillo-Rodríguez, 2008; Graczyk et al., 2021; Vaseghi et al., 2021). Although the neurobiology of cannabis use for sleep is still under investigation, CB1 receptors are highly concentrated in brain regions implicated in the sleep-wake cycle, such as the hypothalamus, hippocampus, and basal ganglia (Murillo-Rodríguez, 2008; Vaseghi et al., 2021). In this regard, ECS regulation of sleep-wake related neurotransmitters, may also have a larger role in the known mechanisms of sleep and arousal. In turn, manipulation of the ECS through cannabis use may explain its perceived therapeutic benefits for sleep. As this manipulation may directly reduce physiological arousal, these findings may further clarify why individuals with high rates of baseline insomnia severity in our study demonstrated greater perceived symptom improvement with cannabis use. Taken together, our results suggest that it may be worth investigating cannabis use in individuals with more severe presentations of insomnia. Future clinical studies may focus on targeting this specific population.

Beyond insomnia, we also investigated depression and anxiety more thoroughly in chapters 4 and 5. In both studies, we observed differences across conditions in response to cannabis use. In chapter 4, although cannabis was generally perceived to be efficacious, it was observed that individuals with insomnia in depression reported CBD-dominant strains to be significantly less efficacious than other strains. The same result was not observed in the anxiety and comorbid conditions, leading us to theorize that distinct symptom profiles may contribute to an individual's response to cannabis. With respect to the role of insomnia in these conditions, we referenced a study that explored the association of insomnia with anxiety and depression in a community-based sample of

1014 individuals (Johnson et al., 2006). In this study the predominant pattern in the directionality of associations between insomnia and these disorders moved from anxiety to insomnia, and from insomnia to depression. Lesser observed pathways moved from insomnia to anxiety, and from depression to insomnia. Interestingly, the associations were adjusted in the presence of co-morbid anxiety and depression, suggesting distinct relationships between insomnia and these conditions (Johnson et al., 2006). These findings may have further implications on how treatments for comorbidities can be approached. In our research examining responses to cannabis, we also noted converse trends in symptom improvement between insomnia and depression. In chapter 5, we reported that in contrast to individuals with insomnia, those with higher baseline depression severity were less likely to report symptom improvement following cannabis use, while individuals with lower baseline depression severity were more likely to report symptom improvement. The role of pre-symptom severity in anxiety, however, was less clear. These results demonstrate that there may be distinct biological mechanisms at play that lead to differences in relation to individual symptom profiles, and the apparent symptom-specific nature of cannabis use.

Taken together, our findings provide the fundamental groundwork required for further investigation of the therapeutic properties of cannabis for mental health. On a grander scale, our research also has the potential to inform both the evaluation of existing cannabis frameworks, and the development of future cannabis policies and regulations.

6.3 Limitations

While the studies covered in this thesis can contribute to the evolving research landscape of cannabis therapeutics, they are not without limitations. The following section will highlight the major limitations of the collected works. Additional limitations of each study are summarized in greater detail within the relevant chapters.

6.3.1 Self-Reports of Conditions and Symptoms

A major point of consideration when interpreting the findings of our research is the subjective reporting of user conditions and symptoms. As per the nature of how our data were collected, individuals were prompted to record conditions and symptoms, and evaluate severity of symptoms as they perceived them. This poses limitations regarding the reliability and validity of the reported mental health concerns. It is likely that the symptoms made available for selection were interpreted by individuals to be interchangeable with clinical conditions. This is especially relevant in the context of mental health, as general audiences will often synonymously use the terms “depression”, “anxiety” and “insomnia”, to define “sadness”, “worrying” and “sleep troubles”. Moreover, measurements of severity remained the same, regardless of the exact condition or symptom an individual reported. Perceptions of symptoms likely varied from one individual to the next, which may have further influenced severity ratings. In contrast, formal diagnoses can capture many of the different manifestations of clinical conditions, and validated measures can more accurately assess symptom severity.

6.3.2 Examination of Strains

Cannabis is a complex plant, and the contribution of a multitude of factors produces the effects that are often associated with the drug. Throughout this thesis, we discussed how different components of cannabis can lead to large variations in an individual's perceived response to the drug. Although two of our studies compared perceived effects between strain categories, previous research has typically dismissed differences in responses between commercial strains, as they are often regarded to be based on unsubstantiated claims (Russo, 2019; Schwabe & McGlaughlin, 2019). To some extent, there is a valid argument to be made with this point. An exploration of THC and CBD content would have provided a more valuable picture of how different formulations can drive these perceived effects, but we did not examine this further as available product data were prepopulated and varied greatly between licenced producers. Furthermore, our data lacked additional information on other cannabis constituents. As we were unable to accurately assess the effects of cannabinoid content, we instead focused on examining strain categories to provide more insight on how consumer choices and response expectancy may have influenced user reports. While this information is valuable in its own right, it cannot be used to make definitive conclusions on whether individual strains are more or less beneficial for specific conditions or symptoms.

6.3.3 Additional Factors

Importantly, data collected for our research did not allow for the examination of additional contributing factors of cannabis response. Our studies were limited to app-

collected data, which did not include user information beyond age and gender. Information such as sex, weight, medical history, and comorbid conditions were not obtained from users. Additional cannabis use-related information, such as user tolerance, negative experiences, and adverse effects, were also not collected. This greatly narrowed the avenues of cannabis use that we were able to explore and limited the conclusions that we were able to make with our research. An ideal manner of investigating mental health would be multidimensional, acknowledging the many factors that can influence outcomes. Although this is not always possible, evaluations of potential treatments should aim for a balanced approach toward understanding the therapeutic benefits of cannabis alongside associated risks. As the nature of our data did not allow for this type of evaluation, our results must be interpreted with caution.

6.3.4 Convenience Sample

Gathering information through mobile apps is a straightforward method of expediting data collection, but there is an inevitable trade-off to be made between efficiency and representativeness. This type of data collection is inherently biased, as it focuses on convenience over the balanced representation of a population. The current thesis includes studies using convenience samples of individuals who monitored their cannabis use through a cannabis tracking app. While the app is publicly available for age-appropriate use in Canada, it is primarily marketed toward regular cannabis users looking to improve therapeutic outcomes with cannabis use. As such, expectancy bias may have influenced at least some of the positive findings reported in the studies. Large effect sizes

should consequently be regarded as the combined effect of the pharmacological properties of cannabis, and individual response expectancies. This also raises an additional limitation around biased samples that requires consideration. As individuals using the app were likely not cannabis-naive users, it is possible that the samples included in this work overrepresented individuals who responded well to cannabis use, and underrepresented individuals who found cannabis to be ineffective for therapeutic purposes. In other words, the samples may have disproportionately represented individuals benefiting from cannabis use. The resulting findings are therefore not generalizable to larger populations and may not accurately reflect the true effects of cannabis use for the management of sleep and mental health conditions.

6.4 Priorities and Considerations for Future Research

6.4.1 Elucidating Cannabis Mechanisms of Action

Several studies have reported antidepressant, anxiolytic, and sleep-inducing properties of cannabis, yet the mechanisms that contribute to these pharmacological actions are less understood. Despite its potential benefits, research on its use for mental health is varied. In depression, cannabis use has been associated with both positive and negative effects on depressive symptoms (Fernández-Ruiz et al., 2020; Sarris et al., 2020; Navarrete et al., 2020; Graczyk et al., 2021). Previous research has reported benefits with acute use, but greater levels of depressive symptoms in extended, heavy use (Navarrete et al., 2020; Sarris et al., 2020; Graczyk et al., 2021). Similar findings have been reported in anxiety, with cannabis use at lower doses having anxiolytic effects, while higher doses

have been associated with increased anxiety (Van Ameringen et al., 2020; Graczyk et al., 2021). In the case of mood and anxiety, researchers have theorised that ECS interactions with the prefrontal cortex and specific structures of the limbic system (particularly the amygdala and hippocampus) may have modulating effects on mood and anxiety (Turna et al., 2017; Navarrete et al., 2020; Sarris et al., 2020). As described extensively in chapter 2, various formulations of cannabis have also demonstrated some positive effects on sleep outcomes. In recent years, phtyocannabinoids such as THC and CBD have even been reported to work in tandem with terpenes (constituents responsible for the aroma of cannabis) to produce some of the desired effects attributed to the plant (Sommano et al., 2020; Ferber et al., 2020).

As discussed in our research, many of the varying responses to cannabis are often linked to the dose and formulation of individual cannabis products. With respect to the involvement of phytocannabinoids, studies have reported anxiolytic and antidepressant effects with CBD (Crippa et al., 2018; García-Gutiérrez et al., 2020). The effects of THC, however, seem to be largely dose-dependent, and research on depression, anxiety, and sleep have noted symptom improvements with low doses of THC and worsening symptoms with high doses of THC (Navarrete et al., 2020; Sarris et al., 2020; Fernández-Ruiz et al., 2020). Interestingly, a few studies have also demonstrated partial inhibition of some of the negative effects associated with THC when used in combination with CBD. This finding was also highlighted in our review of cannabinoids for sleep. As the interactions between these compounds and their associated effects can be relatively

complicated, this presents a unique opportunity for future studies on cannabinoid interactions.

Much of the existing literature on therapeutic cannabis reports several limitations across studies. Since high-quality evidence in favour of therapeutic cannabis is sparse, current recommendations generally advise against the use of cannabis for these conditions (Allan et al., 2018; Borodovsky & Budney, 2018; Stanciu et al., 2021; Tourjman et al., 2022). This greatly limits the ability of health professionals to make informed choices about prescribing cannabis. If considered for therapeutic use, prescribers are often required to monitor the long-term effects of cannabis and assess benefits and harms at both individual and societal levels (Juurlink, 2014; Allan et al., 2018). As such, recommending or prescribing cannabis for mental health demands a careful balance of both the benefits and harms of the drug. Although the clinical potential of cannabis is promising, it should be noted that the ubiquity of the ECS adds an additional layer of complexity to drug development. Because of its broad effects on the central nervous system, targeting specific symptoms without the side effects that are so often associated with cannabis use has proven to be rather difficult. In fact, this dichotomous behaviour is thought to be the reason acute cannabis use may alleviate symptoms, while chronic use may disrupt ECS activity and intensify symptoms (Alger, 2013; Sarris et al., 2020; Fernández-Ruiz et al., 2020). Nevertheless, the widespread actions of the ECS may provide an explanation for its particularly positive effects on comorbid mental health concerns. In this regard, understanding the neurobiological mechanisms of the ECS, may very well be the key to unlocking the full therapeutic power of cannabinoids.

6.4.2 Reviewing Commercial Cannabis Product Regulations

As noted in chapter 3, cannabis plants as we know them today are the products of many years of interbreeding. While biochemically distinct species of cannabis do exist, available products in the commercial marketplace do not distinguish between species. Instead, these products highlight strain categories such as “sativa” and “indica”, despite often being highly hybridized varieties of the *Cannabis sativa* and *Cannabis indica* species (Russo, 2019; Sholler et al., 2022). Perhaps more concerning, is how these products are marketed to the public. For example, a study investigating advertising claims of CBD products available in Canada reported that 53.3% of the product descriptions contained at least one medical or therapeutic claim (Zenone et al., 2021). The ability to treat or manage anxiety was among the most prevalent claims for these products (Zenone et al., 2021), despite recent research noting that findings from clinical trials are equivocal at best (Van Ameringen et al., 2020). Among recreational users, cannabis attributes, such as strain categories, are commonly associated with unique physical and therapeutic effects (Stith et al., 2019; Zhu et al., 2021; Sholler et al., 2022). Although the consensus among most researchers is that these effects are more likely the result of interacting cannabinoids and other minor constituents, products are often marketed such that only strain categories and the ratio of THC to CBD are reported to consumers (Vandrey et al., 2015; Piomelli & Russo, 2016; Russo, 2019).

In recent years, researchers have used biochemical assays to analyze the exact chemical properties of commercially available cannabis products. These studies have frequently reported inconsistences between product labels and content (Vandrey et al.,

2015; Schwabe & McGlaughlin, 2019; Stith et al., 2019). In some studies, products labelled as different strains had similar concentrations of major cannabinoids, but varying terpene concentrations (Russo, 2011; Sholler et al., 2022). Other studies observed characteristic differences between labs in similarly labelled products (Jikomes & Zoorob, 2018; Schwabe & McGlaughlin, 2019). As it stands, the accuracy of cannabis product labels is largely dependent on the manufacturer, supplier, and distributor; however, the cannabis contents of commercial products are not verified in a standardized or reliable manner (Schwabe & McGlaughlin, 2019; Kees et al., 2020). This becomes a much larger concern in the context of public health, as consumers with preconceived perceptions of strain categories will use these labels to purchase products specifically for their expected therapeutic effects (Piper, 2018; Schwabe & McGlaughlin, 2019; Luc et al., 2020; Zhu et al., 2021).

Herein lies the need for more stringent regulations surrounding commercial cannabis products. First, a fundamental effort should be made to understand and classify cannabis products by their chemical composition (Koltai et al., 2019; Kees et al., 2020). This may further involve appropriately grouping comparable cannabis products by genetically profiling and re-classifying existing commercial products. Standards for cannabis advertising should also be re-examined. In a recent study, several cannabis-related attributes were evaluated to understand their relative importance in consumer purchasing decisions (Zhu et al., 2021). The researchers found that four out of the top five important attributes that influenced purchasing decisions were intrinsic factors related to the product content or quality. Among these top factors, ‘strain type’ was reported as the

second most important product attribute next to ‘quality’. The authors noted that while research on consumer purchasing preferences was lacking, the consumer experience may have larger implications on cannabis policy. Though our research provides a brief exploration of how consumer perceptions of cannabis products may influence perceived symptom improvement, the extent to which product labels may affect perceived experiences is less understood and may also be worth investigating further (Luc et al., 2020; Zhu et al., 2021).

6.4.3 Considerations for Cannabis-Focused Clinical Trials

The landscape around cannabis use has shifted steadily over the last few years, and priorities for research have evolved alongside it. Across our work, we have emphasized the need for placebo-controlled trials, but there are several additional considerations to be made during the initial stages of study design. Randomized controlled trials (RCT) are considered by many as the gold standard for drug development, yet it has been reported that less that 50% of clinical innovations move on to general use (Bauer & Kirchner, 2020). Implementation science has since been established as a means of understanding how empirical evidence from clinical research can be utilized in real-world settings. In essence, it aims to go beyond clinical research to identify strategies for the application of clinical innovations (Bauer & Kirchner, 2020). This, however, poses a unique challenge for cannabis researchers, as cannabis products are already commercially available and widely used for therapeutic purposes. In this way, cannabis researchers are under immense pressure to simultaneously evaluate the efficacy

and effectiveness of the drug, while exploring how the use of the drug may evolve beyond its current applications. These specific objectives cannot be captured by RCTs alone and require additional studies for generalizable results (Porzsolt et al., 2015; Porzsolt & Jauch, 2018; Dal-Ré et al., 2018; Hutchison et al., 2019). Nevertheless, it is critical for clinical trialists to consider the limitations of standard RCTs when designing cannabis studies.

The lack of applicability to real-world conditions is a major criticism of RCT studies. While this critique cannot be completely resolved, some aspects of this may be addressed through study design considerations. For example, placebo-controls have been recognized as a particular challenge of cannabis research because of the absence of expected psychoactive effects and the typical aromas associated with cannabis products (Banerjee et al., 2022). In these instances, researchers might instead consider selecting alternative comparators that can address more specific cannabis research questions (Freedland et al., 2019).

Technological advancements have also introduced additional methods of data collection that are considerably more feasible and can provide researchers with real-time information (Lenze et al., 2021). We highlighted the mobile nature of data collection as a major strength of our work, as it allowed us to investigate cannabis use in naturalistic conditions. Similarly, researchers may be able to strengthen data collection through mobile ecological momentary assessments (EMA) that can capture moment-to-moment changes more precisely (Lenze et al., 2021). The increased feasibility of this type of data collection might also allow for the integration of additional real-world data, such as

electronic health records, and investigations of patient-important outcomes (Hutchison et al., 2019; Perlis et al., 2019; Lenze et al., 2021).

Finally, to truly inform clinical practice, researchers need to be mindful of standard RCT reporting practices (Li et al., 2017; Kwakkenbos et al., 2021). Incomplete RCT reporting can lead to irreproducible results, impaired study validity, and research misconduct (Li et al., 2018). By adhering to common reporting guidelines, researchers can maximize transparency and more accurately present findings that can be used for evidence-based decision-making on cannabis use (Li et al., 2017; Kwakkenbos et al., 2021). A recent extension of the Consolidated Standards of Reporting Trials (CONSORT) has even been developed to guide researchers reporting on RCTs that include routinely collected data, such as electronic health records (Kwakkenbos et al., 2021). Together, RCT considerations such as these may present significant advancements for cannabis-based research and medicine.

6.4.4 Federal Barriers to Cannabis Research

As a final note, it is worth mentioning how federal barriers have limited the progress of cannabis research. Although many of these challenges have also been reported globally in other jurisdictions (Piomelli et al., 2019; Haney, 2020; Cooper et al., 2021), the case of Canadian cannabis research is particularly discouraging. Despite legalization allowing for cannabis to become increasingly more accessible to consumers, federal approvals for clinical trials have lagged, delaying both research advancements and

the development of potential cannabis-based therapies and treatments (Wadman, 2019; Webster, 2021; Rueda et al., 2022).

Though funding has been cited by our US counterparts as a major barrier to cannabis research, Canadian researchers have not had such difficulties. In fact, the Canadian government has funded a multitude of projects focused on cannabis research, with several more organizations and private investors following suit (Dolgin, 2018; Webster, 2021; Rueda et al., 2022). Indeed, our own research team secured government funding in 2019 to conduct an RCT evaluating cannabis treatments for insomnia in depression. Notwithstanding this financial support, Canadian cannabis researchers have faced significant challenges meeting the federal criteria required for clinical trial approval. Canadian cannabis products can currently fall under the domain of either commercial use or research use, yet the regulatory criteria for production vary for each (Rueda et al., 2022). The more stringent requirements are applied to products used for research purposes, barring researchers from studying cannabis without facing years of backlogs (Wadman, 2019; Webster, 2021; Rueda et al., 2022). Furthermore, though the federal government no longer classifies cannabis as a controlled substance, researchers are additionally required to obtain a cannabis research licence, providing detailed information on security and storage of all cannabis products (Rueda et al., 2022). These approval processes have halted cannabis studies so greatly that hundreds of researchers across the country recently signed an open letter to the federal government highlighting the regulations as barriers to research (Webster, 2021). For our own RCT, it has taken nearly four years to meet all federal requirements.

At present, the federal government has acknowledged the regulatory barriers to cannabis research and has clarified some requirements for approval (Rueda et al., 2022). While this development may present a promising future for the field, opportunities for Canadian cannabis research have already been blunted. In some cases, industry partners have pulled support and funding sources have expired (Webster, 2021; Rueda et al., 2022). Nevertheless, there is a clear consensus among Canadian researchers that alternative frameworks for approval need to be explored, and that existing federal restrictions on cannabis research require re-evaluation.

6.5 Conclusion

The research presented in this work demonstrates potential for cannabinoid-based products to be used for the management of various mental health concerns; however, our results should be considered alongside the major limitations of retrospective, app-based studies. Across our work, we observed some favourable responses to cannabis for the management of sleep and mental health. While our findings may be promising, additional research on the safety of cannabinoid-based products is required. Further research will also be necessary to elucidate the exact mechanisms underlying endocannabinoid signalling, and to determine how this information may be best used to inform drug development. Overall, our research illustrates the current Canadian landscape of cannabis use for sleep and mental health and supports further exploration of cannabis as a therapeutic avenue for consideration.

6.6 References

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